EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875** **Honorable Renée Marie Bumb, Chief Judge**
This Document Relates to Gaston J. Roberts, Jr., and wife Jan Roberts | Case No. 1:20-cv-00946-RBK-JS	**EXPERT REPORT OF NADIM MAHMUD, M.D., M.S., M.P.H., M.S.C.E.**

I am an Assistant Professor of Medicine and Epidemiology at the University of Pennsylvania Perelman School of Medicine. I am triple board certified in Internal Medicine, Gastroenterology, and Transplant Hepatology and have significant clinical and research expertise pertaining to chronic liver disease, cirrhosis, liver cancer, including hepatocellular carcinoma (HCC), and pre/post-liver transplantation care. I have been asked to review and respond to the opinions offered by Fareeha Siddiqui, M.D. regarding the potential causes of the HCC experienced by Mr. Gaston J. Roberts, and to provide my independent expert opinion regarding the cause or causes of Mr. Roberts' cancer.

1. Background and Qualifications

My curriculum vitae (CV) is attached as Ex. A to this report. To briefly review my academic background and training, I completed a combined B.S./M.S. degree in Molecular Biophysics and Biochemistry at Yale University in 2008. I completed an M.P.H. degree from the Columbia University Mailman School of Public Health in 2011 and subsequently received my M.D. from Stanford University School of Medicine in 2013. My Internal Medicine internship and residency were completed at Brigham and Women's Hospital in the Harvard Medical School system in 2016. Following this, I began a gastroenterology fellowship at the Hospital of the University of Pennsylvania. During this time, I completed a Master of Science in Clinical Epidemiology (M.S.C.E.) degree in 2019. I then completed an additional fellowship in Transplant Hepatology in 2020, where I deepened my clinical expertise in the care of patients with chronic liver disease, cirrhosis, liver cancer, and pre- and post-transplant care. Since June of 2020, I have worked as a faculty Transplant Hepatologist at

both the Hospital of the University of Pennsylvania and at the Corporal Michael J. Crescenz Philadelphia Veterans Affairs Medical Center through a joint appointment. In my capacity as a Transplant Hepatologist I care for patients across the spectrum of chronic liver disease, including patients with hepatic inflammation and fibrosis in the absence of cirrhosis, patients with cirrhosis resulting from myriad chronic liver disease processes, patients listed for liver transplantation, and patients who require long-term post-liver transplant care.

In addition to my clinical duties, I am a grant-funded clinician-scientist with expertise in cirrhosis, liver transplantation, inflammatory bowel disease, and outcomes research in hepatology and gastroenterology. My research spans large database clinical epidemiology, risk prediction modeling, pharmacoepidemiology, and healthcare disparities, with a strong focus on risk stratification in cirrhosis, metabolic-associated steatotic liver disease (MASLD), and pharmacologic impacts on liver disease progression. I have authored over 145 peer-reviewed publications, including studies addressing HCC diagnosis, management, and outcomes, as well as pharmacoepidemiology studies evaluating the impact of angiotensin receptor blockers (ARBs, such as valsartan) on cirrhosis-related adverse events. I have expertise integrating advanced statistical modeling, causal inference methods, risk prediction modeling, and real-world data analysis to inform clinical decision-making and healthcare policy. I have given invited clinical and research talks at major international liver conferences, including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL). I have also served as first author on major national society clinical guidelines in patients with chronic liver disease and cirrhosis for the American College of Gastroenterology (ACG).

The Hospital of the University of Pennsylvania (HUP) is a high-volume liver transplant center, with over 160 transplants performed in 2024. As part of my role at HUP, I perform liver transplant evaluations, attend weekly transplant selection committee meetings, as well as weekly tumor board conferences where diagnosis and management of patients with liver cancers is the primary focus. I have participated in the care of hundreds of patients with HCC during my training and current faculty position. In this capacity, I have direct involvement in counseling patients with chronic liver disease about the risk factors for liver cancer, screening strategies for early detection and diagnosis of liver cancer, multidisciplinary discussions to determine locoregional, transplant-related, and/or systemic treatments for liver cancer, and post-transplant surveillance for recurrent liver cancer. As a result, I have significant knowledge and expertise with respect to the risk factors that contribute to the development of liver cancers such as HCC.

2. Summary of Opinions

I intend to offer the following opinions in connection with this case:

1. Cirrhosis of the liver, at any stage, is the most well-known and well-established risk factor for HCC. The scientific literature establishes that patients with cirrhosis, and

in particular cirrhosis related to fatty liver disease, have a 30- to 45-fold increased risk of developing HCC, relative to patients without cirrhosis. In addition, the relevant scientific literature establishes that particular chronic liver diseases that lead to cirrhosis and comorbidities associated with cirrhosis—including, but not limited to, metabolic dysfunction-associated steatotic liver disease (MASLD)—are also independent risk factors for HCC, even in the absence of cirrhosis.

2. NDMA exposure is not recognized as a risk factor for HCC within the hepatology community or by any national or international hepatology society. While two epidemiologic studies of valsartan users have detected a weak association between NDMA-contaminated valsartan exposure and liver cancer, these studies are subject to a number of key limitations and biases. In addition, the weak potential association that is reported is dwarfed by the other strong and well-established risk factors for HCC, including cirrhosis, MASLD, obesity, and diabetes.

3. The "differential diagnosis" performed by Dr. Siddiqui—which she claims supports the opinion that Mr. Roberts' use of NDMA-contaminated valsartan is both the "most substantial factor" and the "only substantial factor" in causing Mr. Roberts' HCC—is contrary to established scientific knowledge regarding the risk factors for HCC and is unsupported by the scientific literature.

4. A proper differential diagnosis demonstrates that Mr. Roberts' HCC resulted from his known risk factors for the disease, including, but not limited to, his diagnoses of cirrhosis, MASLD, obesity, and diabetes, each of which predated Mr. Roberts' use of NDMA-contaminated valsartan. Furthermore, there is strong evidence that Mr. Roberts' HCC may have been present at the time of his first exposure to NDMA-contaminated valsartan.

My opinions, which are set forth in more detail below, are based on my review of the available medical records, relevant scientific literature, depositions, reports offered by plaintiff's experts, and other case materials, as detailed in the "Materials Reviewed" section. All of my opinions are held to a reasonable degree of medical certainty.

3. Materials Reviewed

In forming my expert opinions, I have reviewed materials that include, but are not limited to, the following:

A. Mr. Gaston Roberts' Medical Records

- Cardiology Associates records from Dr. Ralph Buckley (cardiologist), dated 11/14/2006 to 3/20/2014
- Eastern Shore records from Dr. Christopher W. Ives (gastroenterology), dated 8/19/2009 to 6/23/2016

- Urology & Oncology Specialists clinical records, dated 4/11/2012 to 12/16/19
- Eastern Shore records from Dr. Darryle P. Bullard (pulmonology), dated 10/26/2012 to 3/3/2014
- Alabama Medical Group records from Dr. Donald B. Sanders, dated 11/4/2015 to 10/30/2019
- Diagnostic and Medical Clinic records from Dr. S. Bennett Hooks III, dated 7/18/2018 to 2/26/2020
- UAB Medicine clinical records, dated 8/16/2018 to 3/3/2020
- Bay Minette records from Dr. Gerald Anthony Sparks, dated 9/27/2019
- Southern Cancer Center records, dated 12/3/2018 (initial consultation) to 2/3/2020
- Thomas Hospital clinical records
- Procedure reports, including ultrasound-guided paracentesis and thoracentesis documentation
- Imaging files and associated reports, with particular focus on the following cross-sectional imaging studies:
    - 4/19/2016 - CT abdomen/pelvis
    - 7/17/2018 – CT abdomen/pelvis
    - 8/7/2018 – MRI abdomen
- Prescription records detailing valsartan use, including dosage, duration, prescribing physician, and refill history

B. Expert Reports

- Report submitted by Dr. Fareeha Siddiqui M.D., dated March 10, 2025
- Supporting exhibits, references, and literature cited in Dr. Siddiqui's report
- Report submitted by Dr. Christopher Mele M.D., dated March 9, 2025
- Supporting exhibits, references, and literature cited in Dr. Mele's report
- Report submitted by Dr. William Sawyer, Ph.D., dated March 10, 2025
- Supporting exhibits, references, and literature cited in Dr. Sawyer's report
- Report submitted by Dr. John Russo, M.D., dated March 10, 2025
- Supporting exhibits, references, and literature cited in Dr. Russo's report
- Report and exhibits submitted by Dr. Victoria Chernyak, M.D., M.S., dated April 8, 2025

C. Scientific and Medical Literature

- Peer-reviewed studies, systematic reviews, meta-analyses, clinical practice guidelines, and regulatory documents relevant to this case, including literature addressing risk factors for HCC, and available literature pertaining to NDMA and possible associations with HCC. This includes, but is not limited to, a detailed review of, in particular:

- Pottegård, Anton, et al., Use of N-nitrosodimethylamine (NDMA) Contaminated Valsartan Products and Risk of Cancer: Danish Nationwide Cohort Study. BMJ. 2018; 362:1-7. doi:10.1135/bmj.k3851;

- Gomm, Willy, et al., N-Nitrosodimethylamine- Contaminated Valsartan and the Risk of Cancer. A Longitudinal Cohort Study Based on German Health Insurance Data. Dtsch Arztebl Int. 2021;118(21):357-362. doi:10.3238/arztebl.m2021.0129; and

- Mansouri, Imene, et al. N-nitrosodimethylamine-Contaminated Valsartan and Risk of Cancer: A Nationwide Study of 1.4 Million Valsartan Users. J. of the Am. Heart Ass'n. 2022; 11(17):e08067. Doi:10.1161/JAHA.122.026739.

D. Additional Case Documents

- Deposition transcripts of Ralph Buckley, MD (cardiologist), Darryl Bullard, MD (pulmonologist), Samuel Hooks, MD (gastroenterologist, advanced endoscopist), Christopher Ives, MD (gastroenterologist), Mark Lockhart, MD (radiologist), Jan Roberts (wife of Mr. Roberts), Robert Robichaux, MD (cardiologist, electrophysiologist), Donald Sanders, MD (internist)
- Supporting exhibits accompanying the above depositions
- Death certificate for Mr. Gaston James Roberts, Jr.

If additional materials become available, I reserve the right to update my opinion accordingly.

4. Summary of Medical Findings Related to Mr. Roberts

High-Level Overview of Medical History

Mr. Gaston Roberts [GR] was 64-year-old male with a complex medical history including long-standing obesity, hypertension, diabetes mellitus, hyperlipidemia, obstructive sleep apnea (requiring continuous positive airway pressure), coronary artery disease, atrial fibrillation, and metabolic dysfunction-associated steatotic liver disease (MASLD)-related cirrhosis that was complicated by ascites (requiring serial large-volume paracenteses), hepatic hydrothorax, and hepatocellular carcinoma (HCC). Mr. Roberts' HCC was subsequently treated with locoregional therapies (transarterial chemoembolization [TACE] x3, stereotactic body radiation therapy [SBRT]) and systemic therapy (lenvatinib, nivolumab). Mr. Roberts ultimately succumbed to complications related to decompensated cirrhosis and HCC.

Timeline of Pertinent Medical Events, Diagnostic Findings, and Clinical Management

9/20/2005 – GR obtains a cholesterol panel through Cardiology Associates (Dr. Buckley). This demonstrates a total cholesterol 230, triglycerides 390, and LDL 111.

9/27/2006 – GR obtains labs through Cardiology Associates (Dr. Buckley). AST is 44, ALT is 82 (both elevated).

11/14/2006 – GR is seen at Cardiology Associates (Dr. Buckley). The note reports he has a history of mild CAD diagnosed on CT angiography, **hyperlipidemia** with LDL 153, and obstructive sleep apnea (**OSA**) managed with continuous positive airway pressure (CPAP).

6/22/2007 – GR obtains labs from North Baldwin Infirmary Laboratory. AST is 48. Hemoglobin A1c is reported as either 5.9% or 6.9% (difficult to read). A handwritten note circles the number and reads: "6.9 or 5.9 – if 6.9 refer for poss DM".

12/20/2007 – GR is seen in clinic at Cardiology Associates (Dr. Buckley). His medical history now notes mild **CAD**, **hyperlipidemia**, **OSA** on CPAP, **diabetes mellitus (DM)**, and **hypertension.** Hypertension is being managed with bisoprolol/hydrochlorothiazide at this time.

5/6/2008 – GR is seen at Cardiology Associates (Dr. Buckley). In the plan, he is referred to nutrition for obesity and DM. He is also noted to have a "mild elevated ALT."

5/22/2008 – GR is seen by a clinical dietician at Thomas Hospital Diabetes Center. Body mass index (**BMI**) at the time was recorded as **38.8**, consistent with class II obesity.

11/4/2008 – GR is seen at Cardiology Associates (Dr. Buckley). The impression notes "fatty liver, AST/ALT order given."

- Labs from 11/6/2008 demonstrate: AST 49, ALT 67

7/7/2009 – GR is seen at Cardiology Associates. The impression again notes "elevated LFTs … "refer to GI … Dr. Ives".

8/19/2009 – GR is seen as a new patient visit by Dr. Ives in gastroenterology. He writes that GR "notes that **ever since he was a teenager** in Bay Minette Dr. David Davis used to tell him **his liver numbers were high**. I saw Mr. Roberts in 2000 for the same… He has been told over the years that he **probably has a fatty liver**, i.e. NASH." An ultrasound is ordered. Labs ordered this visit are as follows:

- AST 69, ALT 112, platelet count 174. Fib-4 is 1.99 (**indeterminate range for advanced fibrosis/cirrhosis**).

9/16/2009 – GR is seen in follow-up with Dr. Ives for his abnormal liver tests. He writes: "[a]gain his AST and ALT are 69 and 112 respectively… **Ultrasound demonstrates fatty**

liver." In his impression, Dr. Ives writes: "**[n]onalcoholic steatohepatitis** with no evidence of decompensation… I did discuss liver biopsy with Mr. Roberts who is not really too interested in having liver biopsy."

3/17/2011 – GR is seen in follow-up by Dr. Ives for a history of gastroesophageal reflux disease (**GERD**). GR had several presentations to the emergency department for nighttime regurgitation and aspiration. His GERD was managed with proton pump inhibitor (PPI) therapy. At the time of this visit, GR's medical history noted GERD, irritable bowel syndrome (IBS), **hypertension**, and **obesity** (**BMI was 37.16** at the time). GR had a prior surgical history of cholecystectomy and appendectomy. He reported a **10-year history of smoking**, with a reported quit date on 10/26/1982. At this time GR is taking Diovan for hypertension.

8/7/2011 – GR is seen in clinic at Cardiology Associates. In the chart he carries diagnoses of **hypertension**, **hyperlipidemia**, and mild coronary artery disease.

10/26/2012 – GR is seen by Dr. Bullard in pulmonology for a history of **longstanding OSA** that was originally diagnosed in 2000 and managed with CPAP. At this visit, GR also reported a history of **paroxysmal atrial fibrillation (pAF)** that was diagnosed after "**significant alcohol intake that occurred … at his hunting camp**." At the time of this visit, his medical history additionally noted GERD, hypertension, obesity, OSA, **non-alcoholic steatohepatitis (NASH)**, degenerative joint disease (DJD), coronary artery disease (CAD). Recommendations were made related to CPAP management at this visit.

2/7/2013 – GR has a follow-up visit with Dr. Bullard. Weight was noted to have increased. In addition to ongoing OSA management with CPAP, "weight loss to achieve ideal body weight" was recommended.

3/3/2014 – GR is seen in follow-up with Dr. Bullard. He reported a 12 pounds weight loss over the prior year. BMI remained in the **class II obesity** range at 37.36. Weight loss to achieve ideal body weight was again recommended.

7/9/2015 – GR is seen again by Dr. Ives for long-standing GERD, which has been symptomatic despite twice daily PPI therapy. At the time of this visit, GR's medical history includes GERD, IBS, hypertension, OSA, NASH, DJD, pAF, CAD, and sick sinus syndrome. **BMI at this visit was 39.00**, consistent with **class II obesity**.

11/4/2015 – GR establishes care with Dr. Sanders (internist) for primary care. BMI at this visit is recorded at 39.59. Medical comorbidities as above are noted, including OSA, pAF, and obesity. Dr. Sanders notes in the impression that GR is "unable to lose weight." Labs at this time demonstrated:

- AST 65, ALT 78, platelet count 137 (thrombocytopenia is defined by platelets <150). **Fib-4 is 3.22 (advanced fibrosis/cirrhosis likely).**

4/4/2016 – GR is seen by Dr. Ives and reports 2 out of 10 pain in the left lower ribs. He notes a family history of pancreatic cancer and is concerned that he could have this diagnosis. An abdominal ultrasound is ordered.

4/19/2016 – GR undergoes a CT scan of the abdomen with and without contrast. This demonstrates (per the Thomas Hospital read): "Peripheral margin of the liver is somewhat lobulated, particularly along the infra aspect of the left lobe. 8 mm focal hypodensity is seen in the right lobe. No other focal liver lesions are seen." Then, in the impression: "Although nonspecific, findings above may be evidence of liver cirrhosis."

7/12/2016 – GR is seen in follow-up with Dr. Sanders. Note is made of elevated blood sugars and glucosuria, and a hemoglobin A1c is ordered to evaluate for possible diabetes. BMI is 37.99 at this visit. **Hemoglobin A1c results at 9.5%, confirming a diagnosis of type 2 diabetes mellitus (DM)**. GR is started on metformin to treat DM.

7/25/2016 – GR is again seen in follow-up with Dr. Sanders. Trulicity is added for management of DM. BMI is recorded as 37.26.

6/23/2016 – GR is seen by Dr. Ives in clinic. Per clinical documentation, the ultrasound and subsequent computed tomography (CT) scan obtained on 4/19/2016 revealed cysts in the liver, for which 4-6 month imaging follow-up was recommended. **Ultrasound also demonstrated "fatty infiltration"** and GR's liver function tests **(LFTs) were noted to be "slightly increased."** Per documentation, **GR expressed that "he had been told all of his life that they (LFTs) have been up a bit."** Dr. Ives planned for a repeat CT in 4-6 months.

9/19/2016 – First NDMA-contaminated valsartan prescription is reportedly filled by GR.

10/27/2016 – GR is seen by Dr. Sanders. At this time, **thrombocytopenia is noted**; per documentation by Dr. Sanders: "**his platelets are low and I'm not sure why**... He's not on any medications that could be causing this and in looking back this was not a problem during his last CBC." Additionally, **liver enzymes** were noted to be "slightly elevated, but they've **always been elevated according to the patient**." Hemoglobin A1c was 6.1% at this time. GR reportedly lost about 16 pounds, and BMI was recorded as 35.44, consistent with **class II obesity**.

6/19/2017 – GR is seen by Dr. Sanders. GR reports a 30 pounds weight gain since prior visit, and weight loss was again emphasized. **Thrombocytopenia is again mentioned**. Labs at this time demonstrated:

- AST 44, ALT 58, platelet count 127. **Fib-4 is 2.78 (advanced fibrosis/cirrhosis likely).**

9/21/2017 – GR is seen by Dr. Sanders, who notes that GR "has not been able to lose weight. Diet efforts have been unsuccessful."

5/10/2018 – GR is seen by Dr. Sanders, who plans to "check CBC today for thrombocytopenia."

7/18/2018 – GR is seen in consultation by Dr. Hooks (gastroenterology) as a follow-up to an emergency room presentation from the day prior. GR experienced an "acute onset left upper quadrant epigastric abdominal pain that went through to his back." He was told that "he had **splenomegaly and possibly changes of cirrhosis of the liver**. He was found to have elevated LFTs and elevated total bilirubin." Dr. Hooks was concerned that "he may have a stone lodged in his distal bile duct," possibly related to Trulicity. Numerous laboratory studies related to chronic liver disease are ordered. Pertinent labs, imaging, and procedures near this time demonstrated:

- 7/17/2018 labs: alkaline phosphatase 178, AST 440, ALT 429, total bilirubin 4.0, platelet count 138.
- 7/17/2018 abdominal ultrasound: liver is enlarged and increased in echogenicity consistent with **fatty infiltration**. Vague hypoechoic area measuring up to 3.9cm.
- 7/17/2018 abdominal CT: liver is "generous in size, has a **lobulated contour**." The **spleen is enlarged** measuring 17.3 x 4.9cm. Impression: Hepatosplenomegaly and evidence of diffuse hepatic parenchymal disease, **likely cirrhosis**.
- 7/18/2018 chronic liver disease-related labs: alpha-1 antitrypsin level 181, IgG 624, anti-mitochondrial antibody negative, anti-smooth muscle antibody negative, hepatitis B surface antibody >11.5, hepatitis B surface antigen nonreactive, hepatitis B core antibody non-reactive, hepatitis A antibody non-reactive, ceruloplasmin 31, iron saturation 59%, ferritin 57.2, HFE gene mutation analysis negative.
- 7/18/2018 additional labs: lipase 41, AST 188, ALT 273, total bilirubin 0.6.
- 7/19/2018 endoscopic ultrasound and esophagogastroduodenoscopy (EGD): "erythema throughout the stomach which may be **portal hypertensive gastropathy**." Additionally, "at the proximal antrum there were 3 polyps … had the appearance of polyps (that may be associated with) … portal hypertension." On endoscopic ultrasound, there was "no evidence of choledocholithiasis … abnormal liver test may be from sphincter of Oddi type II… or it could be from a stone that had passed."
- 7/25/2018 labs: alkaline phosphatase 145, AST 66, ALT 79, total bilirubin 1.1.
- **8/1/2018 labs: alpha fetoprotein (AFP) 187.8**; Dr. Hooks comments that GR "needs ASAP referral to Tumor Clinic at UAB."

8/7/2018 Abdominal MRI results (Infirmary Saraland read from Jack Cunningham, MD) – In the impression, he notes: "Pair of masses in the right hepatic lobe are **highly concerning for HCC, especially in the setting of cirrhosis**."

8/7/2018 Abdominal MRI results (UAB read from Mark Lockhart, MD) – The liver has "**cirrhotic morphology with surface nodularity**" and there is "**splenomegaly, consistent with portal hypertension**." The "multiple hyperenhancing hepatic masses with washout

and pseudocapsule are highly suspicious for **multifocal HCC**." Regarding these lesions, the anterior hepatic segment lesion measured 3.7 x 3.4cm and the interlobar region mass measured 5.9 x 4.5cm. There was an additional right hepatic lobe lesion with arterial hyperenhancement and delayed washout at the inferior tip that was "poorly marginated and difficult to reliably measure." Finally, there was a lesion "without arterial hyperenhancement, but with washout on the portal venous phase" that measured 3.2 x 2.8cm adjacent to the hepatic veins and IVC.

8/16/2018 – GR is seen by Mary Comeaux CRNP and Dr. Jared White at UAB in hepatology. This is a new patient visit for **"evaluation and treatment of a liver mass in the setting of NASH cirrhosis."** Mary notes that a mass was found during work up for elevated bilirubin levels. 8/17/18 MRI showed "cirrhosis and a 5cm right posterior liver segment lesions that is ill defined as well as a similar-appearing 5.8cm anterior segment lesion." Per documentation, "these lesions were not obvious on a 7/17/18 single phase CT. Lesion may be visible on 7/1/18 US." Mary further notes that "(GR) reports he was told years ago that he had elevated liver enzymes but not to worry… Work up for cirrhosis is essentially negative; however, he has a hx of DM, HTN and central obesity." In the assessment and plan, Mary summarizes GR's case as "a 62 year old male **NASH cirrhosis** and **two hepatic lesions** w/total tumor diameter 10.8cm **in the setting of cirrhosis** and elevated AFP **concerning for HCC**." A plan was made to review GR's imaging at tumor board and to consider liver-directed therapies given that liver synthetic function was well-preserved (calculated MELD score 8). Relevant labs near this visit include:

- 8/22/2018 – AFP 183 (a tumor marker associated with HCC, elevated), CA 19-9 18 (a tumor marker associated with bile duct cancer, normal).

9/6/2018 – GR is seen in consultation with Lauren Tucker PA in interventional radiology. He is noted to have NASH cirrhosis and multifocal liver lesions consistent with HCC on recent MRI. Lauren writes that "tumor board recommendation from 8/24 is for TACE with destination therapy to be determined after TACE." Note that TACE stands for transarterial chemoembolization.

9/7/2018 – TACE is performed at UAB. Angiographic findings demonstrated multifocal HCC involving segments five, six, and eight. The intervention consisted of "lobar therapy of (the) right hepatic lobe." A repeat MRI in 4-6 weeks was recommended to assess adequacy of embolization and potential need for further treatment.

10/10/2018 – GR is seen by Mary Comeaux CRNP for post-TACE follow-up. She notes that CT scan from 10/10/2018 "shows residual disease and a new 2cm medial seg HCC. No chest mets on staging chest." In her assessment and plan, Mary states that GR is a "63 year old male with **NASH cirrhosis and multifocal HCC**, now s/p TACE." She further states that GR is "not a candidate for liver transplant due to tumor burden beyond downstaging." The documented plan is for repeat TACE followed by consideration of

systemic chemotherapy. Imaging reports referenced in the clinic note are as follows:

- 10/10/2018 CT chest: no evidence of metastases in the thorax.

- 10/10/2018 MRI abdomen: post-TACE changes in segment VIII, with persistent nodular rim arterial enhancement along the medial posterior aspects, suspicious for residual disease. Post-TACE changes in segment VI extending into segment V, with persistent heterogeneous arterial enhancement, highly concerning for residual disease. New 2cm lesion in segment VIII suspicious for HCC. Cirrhosis and splenomegaly.

10/10/2018 – GR is seen in interventional radiology clinic by Dr. Michael Larson. He notes the history of "**NASH cirrhosis and multifocal HCC**" treated with "right lobar chemoembolization." GR's MELD score is reported to be 8, and he has a functional status ECOG 0. The plan is made for repeat TACE for residual HCC.

10/18/2018 – TACE is performed to segments V and VII.

11/21/2018 - GR follows up in interventional radiology clinic. He reports feeling well after his second TACE procedure. Imaging reports referenced in this clinic visit include:

- 11/21/2018 MRI abdomen: the "liver is cirrhotic with sequela of portal hypertension including splenomegaly and a few small varices." There are post-TACE changes in segment VIII with mild persistent enhancement, and post-TACE changes in segment V with persistent heterogenous arterial enhancement, though decreased from prior; these findings are reported to be "combinations of residual disease and posttreatment perfusional abnormalities." There is also a 2cm arterially enhancing lesion in segment VIII that is again noted, without corresponding washout, that "remains concerning for HCC."

12/5/2018 – GR is seen for initial consultation with Dr. William McEvoy, oncologist, at Southern Cancer Center. In his impression, he notes "**stage IIIA HCC"** and "**cirrhosis secondary to non-alcoholic steatohepatitis**." He recommended initiating systemic therapy with Lenvatinib 8mg daily.

12/18/2018 – GR is seen by Dr. Sanders. He notes that GR now has "liver cancer-4 tumors… treated at UAB with chemo injections via catheter in the tumor." Labs at this time demonstrated:

- AST 43, ALT 44, platelet count 126. **Fib-4 is 3.19 (advanced fibrosis/cirrhosis likely).**

2/20/2019 – GR is seen by Mary Comeaux CRNP in follow-up for his "**NASH cirrhosis complicated by HCC**." She notes that GR was started on Lenvatinib on 12/14/2018. GR reports that he is tolerating this medication without any side effects. On MRI, she notes a stable 2cm HCC in segment VIII, but no new disease. The plan is to continue Lenvatinib

and hold off on any additional liver-directed therapy for the time being. Imaging results referenced in this clinic note include:

- 2/20/2019 MRI abdomen: multiple ablation defects within the right hepatic lobe, but without definite residual intralesional enhancement. Stable 2.0cm lesion in segment VIII, consistent with HCC. Cirrhosis with splenomegaly.

5/20/2019 – GR is seen by Mary Comeaux CRNP. GR reports feeling very fatigued and that he has right rib pain. MRI results are noted to reveal a new bland portal vein thrombus with SMV extension. AFP has risen to 56 from 39 previously. MELD-Na score is increased to 12; MELD was 7 on 2/20//2019. GR's fatigue is attributed to Lenvatinib, and worsening liver tests attributed to "Lenvatinib versus progression of liver disease." The plan is to review updated imaging with the Tumor Board and to consider stereotactic body radiation therapy (SBRT) given concern for persistent disease with rising AFP. Imaging results referenced at this clinic visit include:

- 5/22/2019 MRI abdomen: interval development of bland-appearing nonocclusive thrombus in the right and main portal veins, as well as distal SMV. Multiple ablation defects in the right hepatic lobe without definite residual enhancement. Segment VIII HCC slightly decreased in size to 1.6cm. Cirrhosis with splenomegaly.

6/28/2019 – GR is seen in consultation with Dr. Rojymon Jacob in radiation oncology. He notes that GR is a "63yoCM with **long history of known 'fatty liver.'** Diagnosed in August of last year and now s/p TACE x2 but with residual biochemically evident disease… segment V lesion likely responsible for the continued elevation of AFP. " In his assessment and plan, Dr. Jacob writes that GR experienced "**HCC arising out of NASH cirrhosis.**" A plan is made to pursue SBRT targeted to the untreated lesion.

7/10/2019 to 7/15/2019 – SBRT is performed with Dr. Jacob.

8/2/2019 – GR is seen by Dr. McEvoy. Mild leukopenia and thrombocytopenia are noted and attributed as "likely related to his cirrhosis." Lenvatinib is continued.

8/7/2019 – GR is seen by Dr. Sanders. He notes that GR "finished radiation and chemotherapy at UAB."

9/27/2019 – GR seen at Southern Cancer Center. He notes low-grade fever, chills, and myalgia. Lenvatinib is held for two weeks.

10/11/2019 – GR is seen by Dr. McEvoy. Lenvatinib is restarted.

10/17/2019 – GR is seen Mary Comeaux CRNP to follow-up after SBRT. GR reported an emergency room presentation to receive fluids after "getting dehydrated due to excessive heat" while fishing and hunting. He also noted some abdominal and lower extremity

swelling. Mild new-onset ascites was noted. MRI identified at least two new lesions with arterial hyperenhancement concerning for recurrent tumor. The plan was for repeat Tumor Board discussion and consideration of repeat TACE. Imaging results referenced at this clinic visit include:

- 10/16/2019 MRI abdomen: cirrhotic liver with splenomegaly redemonstrated. At least two lesions demonstrate arterial hyperenhancement with washout, concerning for recurrent tumor.

10/30/2019 – GR is seen by Dr. Sanders, who notes that "he has liver cancer with metastases and has lost 21 pounds with chemotherapy."

11/5/2019 – Selective TACE of multifocal right lobe lesions is performed.

11/23/19 – GR presents to the emergency department with increased abdominal distention. He receives paracentesis with 3.5L removed.

11/30/2019 – GR is seen by Dr. McEvoy and reports not feeling well. Blood pressures are reported to be low and there is concern for urinary tract infection. GR is given antibiotics. In light of progression of disease on recent MRI, Lenvatinib was stopped and nivolumab was started.

12/4/2019 – GR is seen in interventional radiology clinic with Dr. Vistasp Daruwalla for post-TACE follow-up. He reports that after recent TACE GR "stopped taking Lasix and redeveloped ascites which required multiple paracentesis." GR reports fatigue and abdominal pain from the ascites. Repeat MRI does not demonstrate any residual lesion. Dr. Daruwalla states in his assessment and plan that GR is a "64-year-old male with history of **NASH cirrhosis and HCC**."

12/4/2019 – GR is also seen by Mary Comeaux CRNP. She also notes GR's further decompensation with ascites that now requires large-volume paracenteses (LVPs). GR reports losing muscle mass. The plan is for an intensified diuretic regimen and ongoing imaging surveillance, as MRI at this time shows no definite residual/recurrent HCC. Imaging referenced during this visit includes:

- 12/4/2019 MRI abdomen: Multiple ablation defects in the right hepatic lobe. No definite findings of residual/recurrent tumor. Hepatic cirrhosis with portal hypertension and splenomegaly noted, as well as moderate-volume ascites.

12/13/2019 – GR is seen by Dr. McEvoy. He notes recommendation from UAB to stop nivolumab. ECOG performance status is recorded at 1.

1/6/2020 – GR is seen by Dr. McEvoy. He notes a recent hospitalization for spontaneous bacterial peritonitis (SBP) in the setting of decompensated cirrhosis. He was treated with

antibiotics, and diuretics were adjusted during hospitalization for ascites. Dr. McEvoy notes that "**Mr. Roberts' recurrent ascites is secondary to his decompensated cirrhosis**."

2/3/2020 – GR is seen by Dr. Jones at Southern Cancer Center. A goals of care conversation is noted.

3/3/2020 – GR is seen by Mary Comeaux CRNP. GR recently had a fall in the bathroom. He reports poor appetite and ongoing weight loss of 26 pounds since prior visit. He reports "sleeping a lot…about 50% of waking hours on some days" and he was recently started on lactulose BID; however, this did not improve his energy levels. MRI demonstrates a moderate right-sided pleural effusion and post-ablation changes in the right hepatic lobe without evidence of recurrence. Mary states she does not "think (GR) would tolerate any liver-directed or systemic therapy." A plan was made for thoracentesis and continued LVPs. Imaging referenced during this visit includes:

- 3/3/2020 MRI abdomen: moderate right pleural effusion, mild ascites in the abdomen. Post-ablation changes of multifocal HCC in the right hepatic lobe without evidence of local recurrence. The liver is cirrhotic in morphology.

3/5/2020 to 3/17/2020 – GR presents to the Thomas Hospital emergency department for shortness of breath and a syncopal episode. Earlier in the day, he had undergone his first thoracentesis (2.8L removed from right pleural space) and a paracentesis (2L removed). On chest X-ray, providers were concerned for a right pneumothorax versus moderate right-sided pleural effusion. A pigtail catheter was placed in the right pleural space, and "blood began to drain from the thoracostomy site." He was then diagnosed with a hemothorax, and subsequently received procedural sedation and a thoracotomy tube. A total ~3L of blood was reported to have drained from the chest. Massive transfusion protocol was initiated. GR was intubated and admitted to the hospital. He was extubated on the following day, however his subsequent hospital course notes that he had significant issues with altered mental status (AMS) with combative behavior in the evenings. Notes state that there was "difficulty getting ammonia levels down." Several goals of care conversations were referenced, including consideration of hospice. On 3/14/2020, GR developed worsening shortness of breath, with "percutaneous air advancing up his neck." His code status was changed to Do Not Resuscitate (DNR). He was given IV morphine to control symptoms. With worsening shortness of breath through 3/17/2020, medication doses were increased for comfort, and GR passed away peacefully at 19:45.

5. Expert Opinion

Dr. Siddiqui's opinion that Mr. Roberts' use of NDMA-contaminated valsartan was a substantial factor in causing his HCC is scientifically and clinically unsound, as are her assertions that Mr. Roberts' use of NDMA-contaminated valsartan is the "most substantial" and "only" factor in causing Mr. Roberts' HCC. Instead, it is my medical opinion that Mr.

Roberts' HCC resulted from advanced fibrosis and/or cirrhosis in the setting of long-standing metabolic dysfunction-associated steatotic liver disease (MASLD) with metabolic dysfunction-associated steatohepatitis (MASH). As set forth below, cirrhosis is the best-established and most-significant risk factor for HCC, with the relevant scientific literature demonstrating that cirrhosis increases an individual's risk of developing HCC by over 30-fold, relative to individuals without cirrhosis.[1, 2] By contrast, there is no established link between the use of NDMA-contaminated valsartan, at any dose for any length of time, and an individual's risk for developing HCC. While two retrospective studies of valsartan users with NDMA contamination have reported small associations between NDMA-contaminated valsartan use and liver cancer, these studies suffer from major methodological flaws and limitations, and at least one other valsartan study found no increased risk of liver cancer associated with use of NDMA-contaminated valsartan. There is no established causal link between NDMA-contaminated valsartan and HCC, and when weighed against the very real risk factor of advanced fibrosis/cirrhosis (as well as many other medical risk factors) from which Mr. Roberts suffered, the cause of HCC in this case is plainly obvious to any qualified hepatologist. As a result, Dr. Siddiqui lacks a reliable scientific basis to either rule in NDMA-contaminated valsartan use as a cause of Mr. Roberts' HCC, or to rule out his many other well-known risk factors as causes of his disease.

(a) Mr. Roberts' HCC

HCC is a primary liver cancer that arises from liver cells (hepatocytes). As detailed below, the primary risk factor for HCC is cirrhosis, with an approximate annual incidence of ~1-8%,[3] and for this reason, all patients with cirrhosis are recommended to undergo routine surveillance for HCC every six months through the performance of imaging (e.g., ultrasound, CT, or MRI) and alpha fetoprotein (AFP) serology, a tumor marker commonly produced by HCC.[4] Most patients are surveilled with an ultrasound and AFP every 6 months. Findings concerning for possible HCC would include new liver lesions noted on ultrasound and/or abnormally elevated or rising AFP levels. If present, the next step would typically be multi-phase cross-sectional imaging (i.e., CT or MRI) which allows for formal HCC diagnosis. "Multi-phase" indicates that images are taken at multiple timepoints relative to a contrast agent being administered, for instance during a pre-contrast phase, arterial phase, and a delayed phase. HCC has highly characteristic features on properly-performed multi-phase cross-sectional imaging, including: (1) arterial hyperenhancement, (2) washout on portal venous/delayed phase, and (3) enhancing peripheral capsule on delayed phase. Radiologists apply Liver Imaging Reporting and Data Systems (LI-RADS) criteria to liver lesions to classify the likelihood that a given lesion may represent an HCC or other malignant tumor.[5, 6] This ranges from LR-1 (definitely benign) to LR-5 (definitely HCC). In general, to meet LR-5 criteria, an arterially hyper-enhancing lesion must either: (1) be at least 10 mm in size and demonstrate both delayed washout and a peripheral enhancing capsule, or (2) be at least 20 mm in size and demonstrate either delayed washout or a peripheral enhancing capsule. These findings are so specific to HCC that a biopsy is not required; the diagnosis can be made entirely through non-invasive means (i.e., proper imaging). Importantly, LI-

RADS can *only* be applied if a patient has strong accepted underlying risk factors for HCC, including cirrhosis, chronic hepatitis B virus infection, or a prior history of HCC.

Once diagnosed, HCC is typically staged according to the Barcelona Clinic Liver Cancer (BCLC) classification.[7] This ranges from very early stage (0), defined as a single HCC lesion ≤2cm with preserved liver function and good functional status, to terminal stage (D), with end-stage liver function and poor functional status regardless of tumor burden. BCLC stage 0 (very early stage) and stage A (early stage) HCC are potentially curable with the use of resection, ablation, or liver transplantation. Patients are generally within liver transplant criteria if the HCC tumor burden is a single tumor <5cm in size, or up to three tumors each <3cm in size.[8] This is referred to as the "Milan criteria.[9]" Selected patients with stage B (intermediate stage) may potentially be curable with liver transplantation despite initially being outside of Milan criteria, provided that the tumor burden can be sufficiently reduced through the use of locoregional therapies such as transarterial chemoembolization (TACE); this is referred to as downstaging.[8, 10] If the total tumor diameter is greater than 8cm, patients are not eligible for liver transplantation through a downstaging protocol, and treatment of HCC with non-curative intent is generally pursued. This may include treatments such as TACE, stereotactic body radiation treatment (SBRT), and systemic therapies such as tyrosine kinase inhibitors (e.g., Lenvatinib) or immune checkpoint inhibitors (e.g., atezolizumab plus bevacizumab, or nivolumab).[3, 11, 12] Finally, regarding prognosis of BCLC stages, patients with stage 0 or stage A disease generally have >5 year median survival, whereas stage B patients who are not candidates for transplant have survival in the range of 10 to 30 months.[13] Patients with stage D disease have median survival of about 3 months and accordingly are not eligible for locoregional or systemic therapies.[7]

In the case of Mr. Roberts, his HCC was formally diagnosed on his 8/7/2018 MRI of the abdomen (note that in subsequent sections I explain that Mr. Roberts' HCC may have initially developed quite some time prior to this). As stated in the imaging report from Dr. Mark Lockhart, the imaging was consistent with multifocal HCC, with at least two confirmed HCC lesions, one 3.7cm x 3.4cm and another 5.9 x 4.5cm in size. (*See* GRobertsJr-PPR-000106.) There were additional lesions that were noted that likely also represented HCC, although they could not be confirmed based on imaging criteria at the time (discussed in more detail below). AFP was elevated to 183, which is also consistent with HCC. Based on the total diameter of the HCC lesions noted on MRI, the lack of metastases on his CT chest imaging, and knowledge that Mr. Roberts' liver synthetic function and his functional status were good at the time of diagnosis, he would have been staged as **BCLC B but outside of liver transplantation criteria**. In my estimation, he was treated appropriately for his HCC, with non-curative intent. He received locoregional therapy with TACE on two occasions to reduce his tumor burden as best as possible, followed by SBRT to address visible residual disease. As his burden of disease progressed, he was initiated on systemic therapies, initially with lenvatinimib and later with nivolumab. Ultimately his clinical course was in line with typical progression for patients with BCLC stage B disease who are outside of transplant criteria. His survival time from formal diagnosis was approximately 17 months, which is in the range of the 10-to-30-month survival estimates noted above.

(b) Mr. Roberts Had Multiple Established Risk Factors For HCC

(1) Cirrhosis

Background

Cirrhosis refers to a condition where the liver develops significant scarring to a degree that impacts the normal function of the liver, which can ultimately lead to liver failure. Within cirrhosis, there is also a spectrum of severity that broadly includes compensated cirrhosis, in which patients are generally asymptomatic, and decompensated cirrhosis, which is characterized by development of major symptoms related to portal hypertension (elevated venous pressures in vessels flowing towards the liver), including ascites (fluid in the abdomen), hepatic encephalopathy (confusion related to the liver), and variceal bleeding (massive bleeding caused by rupture of dilated veins in the gastrointestinal tract).

Scarring in the liver generally accumulates as a consequence of chronic inflammation in the liver, which may occur as a result of many possible causes/etiologies of chronic liver disease. In the United States, the predominant causes of chronic liver disease are metabolic dysfunction-associated steatotic liver disease (MASLD, formerly called non-alcoholic fatty liver disease [NAFLD]) and alcohol-related liver disease (ALD).[14] MASLD is summarized in more detail in the subsequent section and refers to fat infiltration in the liver related to excess body weight (i.e., overweight or obesity) that may result in liver inflammation and scarring over time. Heavy alcohol use is another cause of fat infiltration in the liver that may cause inflammation and scarring, and indeed many patients in the United States have overlapping MASLD and ALD, which has recently been termed "MetALD." In a recent, large national study of veterans with cirrhosis in the United States, among all patients who had fat in the liver (hepatic steatosis) prior to cirrhosis diagnosis, approximately ~30% of patients have MASLD, 30% have ALD, and 30% have MetALD.[15] Apart from MASLD, ALD, and MetALD (collectively called steatotic liver diseases [SLDs]), there are many other potential causes of chronic liver disease and cirrhosis, none of which appear to be relevant to this case. This includes chronic viral hepatitis (hepatitis B virus and hepatitis C virus), autoimmune conditions (autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis), genetic conditions (Wilson disease, hereditary hemochromatosis, alpha-1 antitrypsin deficiency), vascular diseases such as Budd-Chiari syndrome, chronic right-sided heart failure, and rare inborn metabolic disorders typically isolated to pediatric populations, among others.

Chronic liver disease is typically first suspected based on routine blood testing of transaminase levels. These include aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are standard components of so-called liver function tests (LFTs). AST and ALT are enzymes found in liver cells; any process causing inflammation and injury to liver cells will cause AST and ALT to leak out into the blood. Thus, elevated levels may signify a chronic liver disease process. If transaminases are elevated for at least 6

months, this is considered to be "chronic" and further evaluation is warranted to identify the specific cause of chronic liver injury (e.g., MASLD, MetALD, ALD, hepatitis C virus, hepatitis B virus, autoimmune liver disease, etc.). Simultaneously, it is important at this stage to determine the degree of scarring (fibrosis) that is present in the liver. As noted, cirrhosis refers to significant scar tissue that impairs liver function; however, there is a spectrum of scarring/fibrosis that ranges from normal (no fibrosis, termed F0) to cirrhosis (termed F4). The term "advanced fibrosis" generally encompasses patients with F3 or F4 scarring. This staging is usually assessed on liver biopsy, however, in modern practice we have non-invasive means of estimating the degree of liver fibrosis. The current best practice recommendations from major society guidance are to calculate a blood-based fibrosis score called the Fib-4, which is computed using a patient's age, AST, ALT, and platelet count. In patients with MASLD, a Fib-4 <1.3 effectively rules out advanced fibrosis, with a ≥90% negative predictive value.[16-18] This means that out of 100 patients with a Fib-4 <1.3, over 90 of them will truly have no advanced fibrosis. By contrast, a Fib-4 >2.67 denotes a very high risk of advanced fibrosis. Specifically, patients with a Fib-4 >2.67 have a ~80% positive predictive value of having cirrhosis.[16] In other words, among 100 patients with Fib-4 >2.67, about 80 of these patients will truly have cirrhosis based on this test result alone. Of course, additional imaging or blood-based findings may modify the probability of true cirrhosis. For instance, a patient with a Fib-4 >2.67 *and* CT findings supportive of cirrhosis (e.g., nodular ["bumpy"] liver surface and evidence of portal hypertension) has a much higher clinical probability of true cirrhosis than 80%, and in such patients further testing may not be needed to confirm a diagnosis of cirrhosis.[19] Regardless, because of the high risk of cirrhosis indicated by a Fib-4 >2.67, current clinical guidelines recommend that patients with these findings should be referred to a hepatologist for further evaluation and management, which could entail an imaging-based fibrosis assessment (called "liver stiffness measurement" [LSM]) such as transient elastography or MR elastography to confirm the presence of cirrhosis and thereafter enroll in an HCC surveillance protocol (i.e., liver imaging and AFP every 6 months).[20] Finally, patients with a Fib-4 between 1.3 and 2.67 are in an indeterminate range for advanced fibrosis/cirrhosis and should undergo LSM as a next step to determine the likelihood of cirrhosis and inform the need for hepatology referral.[19, 20]

As demonstrated in numerous studies and articulated in national hepatology society guidelines (i.e., American Association for the Study of Liver Disease [AASLD] and the European Association for the Study of the Liver [EASL]), **cirrhosis is the strongest risk factor for developing HCC, regardless of etiology of liver disease**,[21] and cirrhosis is present in 80-90% of patients diagnosed with HCC.[21, 22] Patients with cirrhosis, regardless of the severity of the cirrhosis or the amount of time cirrhosis has been present, have a ~1-8% annual risk of developing HCC,[3, 23] and up to one third of patients with cirrhosis will develop HCC during their lifetime.[24] In recent large population-level data, patients with SLD but without cirrhosis have an HCC incidence rate of 0.14 per person-year, whereas those with SLD and cirrhosis have an incidence rate of 4.29 per person-year (i.e., if 100 patients with cirrhosis were followed for one year, at least 4 would develop HCC).[1] Thus, **cirrhosis confers at least a 30-fold increased risk of HCC relative to patients without cirrhosis**

(this is likely an underestimate given that the comparator was non-cirrhotic SLD in this study). Other meta-analytic studies isolating **patients with NASH/MASH cirrhosis** suggest that the increased risk of HCC attributable to cirrhosis is even higher, **up to a 45-fold increased risk** relative to the absence of cirrhosis.[2] As a result, national and international hepatology society guidelines recommend screening all patients with cirrhosis every six months for liver lesions through imaging (e.g., ultrasound, CT, or MRI) and alpha fetoprotein (AFP) testing, which is a tumor marker frequently produced by HCC.[3, 4] The limited exceptions to this screening guideline include patients with very advanced cirrhosis (known as Child-Turcotte-Pugh class C) who are not transplant candidates, and those with "life-limiting comorbid conditions that cannot be remedied by liver transplantation or other directed therapies," as such patients do not experience survival benefit related to HCC surveillance.[4]

Relevance of Cirrhosis to Mr. Roberts' Case

In the case of Mr. Roberts, **it is very clear that he already had cirrhosis at the time of his HCC diagnosis, which was confirmed on the abdominal MRI from 8/7/2018**. There are many objective lines of evidence that support this. First, on my personal review of the imaging, the 8/7/2018 MRI demonstrates hepatic surface nodularity, which is a "bumpy" appearance to the liver surface that is indicative of the significant scarring observed in cirrhosis. Second, there is splenomegaly on the MRI, which refers to an enlarged spleen related to elevated pressures in the portal vein system "behind" the liver, resulting in congestion in the spleen. These elevated pressures occur in the setting of cirrhosis, where scarring effectively "squeezes" microscopic downstream venous structures of the portal vein (called sinusoids). Third, there is no alternative explanation for portal hypertension and splenomegaly apart from cirrhosis. Alternatives would include significant heart failure, which Mr. Roberts did not have in his medical history, or a portal vein thrombosis (clot) in the absence of cirrhosis, which Mr. Roberts also did not have. Fourth, laboratory studies at this time (and previously) demonstrated thrombocytopenia (low platelet counts, defined as <150). This is an additional supporting criterion, as portal hypertension-induced splenomegaly results in increased sequestration (trapping) of circulating platelets, which results in abnormally low measured platelet counts in the blood. Fifth, the diagnosis of HCC itself provides a strong pre-test probability of cirrhosis—as noted previously, 80% of patients with HCC have cirrhosis. Finally, Dr. Mark Lockhart, a highly-qualified radiologist at UAB (a liver transplant center), states in his imaging report that the liver has "cirrhotic morphology with surface nodularity" and that there is "splenomegaly, consistent with portal hypertension." (Lockhart Deposition, Ex. 2.) Moreover, in his deposition, Dr. Lockhart discusses the application of the LI-RADS classification to the liver masses noted on the 8/7/18 MRI, stating, with respect to multiple lesions, that "[e]verything so far is just fitting all the criteria for LR-5 lesions." (Lockhart Deposition Tr. 33:16-17.) Dr. Lockhart also testified that the MRI findings were consistent with a finding of cirrhosis of the liver (*id*. 46:11-13), that "the LI-RADS criteria cannot be applied unless you have a risk factor such as cirrhosis" (*id*. 49:13-15), and that "in this case, cirrhosis was key to helping make that [HCC] diagnosis" (*id*. 49:19-20).

In addition to the above objective findings, it is apparent that Mr. Roberts' treating physicians were also of the opinion that cirrhosis was present, and **furthermore that NASH cirrhosis was the relevant comorbidity leading to HCC**. Mary Comeaux CRNP initially documented at UAB that Mr. Roberts was being evaluated for "a liver mass in the setting of NASH cirrhosis," ROBERTS-MR-UAB-0001, and, in later notes, stated that Mr. Roberts was being followed for "NASH cirrhosis complicated by HCC." (GRobertsJr-UABHIM-MD-000047.) Dr. Michael Larson, who practices interventional radiology, noted that Mr. Roberts had "NASH cirrhosis and multifocal HCC." (GRobertsJr-UABHIM-MD-000032.) Dr. William McEvoy in oncology wrote in his impression that Mr. Roberts was being managed for "stage IIIA HCC… and cirrhosis secondary to non-alcoholic steatohepatitis." (GRobertsJR-SouCC-000166.) Dr. Rojymon Jacob in radiation oncology noted that Mr. Roberts had a "long history of known fatty liver" (GRobertsJr-UABHIM-MD-000083), and developed "HCC arising out of NASH cirrhosis" (GRobertsJr-UABHIM-MD-000085). Dr. Vistasp Daruwalla, an interventional radiologist, noted that Mr. Roberts had a "history of NASH cirrhosis and HCC." (GRobertsJr-UABHIM-MD-000103.) In many notes from these treating physicians, the model for end-stage liver disease (MELD) or MELD-sodium (MELD-Na) score is also calculated, which is a score that is generally calculated in patients with cirrhosis as an indicator of prognosis. (*See, e.g.*, ROBERTS-MR-UAB-0004; GRobertsJr-UABHIM-MD-000106.) Finally, in Dr. Lockhart's deposition, when asked if HCC was demonstrated in Mr. Roberts' liver (on the 8/7/2018 MRI), he stated: "Yes, that's correct. This was not one of the more challenging studies that I read on a daily basis. Based on the size, the enhancement characteristics, the underlying cirrhosis, I really did not have a lot of… uncertainty." (Lockhart Deposition Tr. 41:24-42:3.) He also confirmed that cirrhosis is an established risk factor for HCC. (*Id*. 46:17-19.) There is no speculation in any notes from any provider that NDMA-contaminated valsartan could be implicated in any way in Mr. Roberts' incident HCC or clinical course. Additionally, as addressed in greater detail below, despite assertions from the Plaintiff's expert witnesses that NDMA is a cause of cirrhosis, there is no scientific evidence to substantiate this claim.

It is obvious that Mr. Roberts had cirrhosis in August 2018. In addition, based on my detailed review of Mr. Roberts' records, it is my medical opinion that he had cirrhosis for at least several years prior to his diagnosis of HCC. There are numerous lines of supporting evidence for this claim. First, Mr. Roberts had long-standing evidence of chronic liver disease, which was ultimately classified as NAFLD/MASLD. Notes from Dr. Ives on 8/19/2009 report that Mr. Roberts stated that "ever since he was a teenager … his liver numbers were high." (*See* GRobertsJr-CA-000661.) Again on 6/23/2016, when discussing Mr. Roberts' elevated transaminases, Dr. Ives wrote that Mr. Roberts reported "he had been told all of his life they have been up a bit." (GRobertsJr-ESMS-000002 (Ives DX4).) An ultrasound performed around 8/2009 also demonstrated "fatty liver," which is noted in Dr. Ives' note from 9/16/2009, where his impression is that "nonalcoholic steatohepatitis" is the cause of Mr. Roberts' elevated liver tests. (*See* GRobertsJr-CA-000654.) These findings indicate long-standing chronic liver disease related to MASLD.

Second, Mr. Roberts had all of the metabolic comorbidities that are associated with MASLD and MASH that increase risk of progression to cirrhosis, including obesity (for much of his history he had class II obesity with BMI >35), hypertension, hyperlipidemia, obstructive sleep apnea, and diabetes mellitus.[25-30]

Third, calculation of Mr. Roberts' Fib-4 demonstrated elevated levels as early as 11/4/2015 (the earliest labs available for review, three years prior to his formal cirrhosis diagnosis), at which time the Fib-4 was 3.22. As noted previously, Fib-4 values >2.67 in patients with MASLD have an 80% positive predictive value for cirrhosis,[31-33] and referral to a hepatologist for further evaluation would have been indicated at that time.[20] Moreover, the Fib-4 was consistently elevated thereafter; for instance, the value was 2.78 on 6/19/2017 and 3.19 on 12/18/2018. Interestingly, the first available Fib-4 calculation on 8/19/2009 was 1.99, representing an indeterminate range for advanced/fibrosis. In modern practice, this would trigger measurement of liver stiffness and consideration of hepatology referral. These results demonstrate that Mr. Roberts had hepatic fibrosis in 2009 that progressed to possible cirrhosis by 11/2015 at the latest, and definite cirrhosis by 4/2016 (detailed below).

Fourth, Mr. Roberts had developed thrombocytopenia prior to his formal diagnosis of cirrhosis in August 2018. As stated, development of thrombocytopenia (values <150) may occur for multiple reasons when cirrhosis develops,[34] including in the setting of splenomegaly related to portal hypertension, reduced liver production of regulators of platelet production (thrombopoietin),[35] and increased platelet destruction.[36, 37] Dr. Sanders, Mr. Roberts' primary care physician, noted on 10/27/2016 that Mr. Roberts' "platelets are low and I'm not sure why… He's not on any medications that could be causing this and in looking back this was not a problem during his last CBC." (GRobertsJr-AMG-000015 (Sanders Ex. 1 at -015).) This is an extremely common pattern in patients who have developed cirrhosis; platelet counts are initially normal, however, with the development of cirrhosis, portal hypertension, and progressive splenomegaly, the platelet count begins to drop. Again, this was noted in 2016, two years prior to Mr. Roberts' formal cirrhosis diagnosis.

Fifth, the cross-sectional imaging performed on Mr. Roberts in April 2016 independently confirmed the presence of cirrhosis. On 4/19/2016, Mr. Roberts underwent a CT of the abdomen and pelvis. The treating radiologist's report states: "My review of this imaging demonstrates a very clear nodular contour of the liver, most notably in the left hepatic lobe." As detailed previously, a nodular ("bumpy") liver surface occurs in the presence of significant scar tissue in the liver, and is the best qualitative indicator of cirrhosis on CT, with >80% specificity.[38, 39] Based on my significant experience in treating patients with cirrhosis and reviewing their radiological scans, I agree with this assessment and am of the opinion that Mr. Roberts' 4/19/16 CT clearly demonstrates the presence of cirrhosis of the liver. The left hepatic lobe is overtly nodular in appearance, in addition to being enlarged along with the caudate lobe. These reflect "lobar redistribution" and are additional signs of cirrhosis on imaging.[40] Additionally, there is recanalization of the umbilical vein on this CT scan (i.e., reopening of a vein that is typically closed in adults due to elevated portal pressures from

cirrhosis),[41, 42] and the spleen size is enlarged by my measurements. Importantly, **experts in radiology offered by both parties in this case confirm that Mr. Roberts had identifiable cirrhosis in April 2016**. The plaintiff's proffered expert, Dr. Christoper Mele, reviewed the 4/19/2016 CT and stated: "images demonstrate an enlarged liver with a nodular surface contour, enlargement of the caudate lobe … an enlarged spleen measuring approximately 16cm … recanalization of the paraumbilical vein … observed in patients with underlying cirrhosis." (Mele Rep. at 2.) Dr. Victoria Chernyak (defendants' radiology expert) reviewed this CT and stated there is "relative enlargement of the left hepatic lobe and nodular liver contour … umbilical vein was recanalized, confirming presence of portal hypertension … consistent with the diagnosis of cirrhosis." (Chernyak Rep. at 3-4.) Finally, Dr. Siddiqui agrees that Mr. Roberts had cirrhosis in 2016, even though she (incorrectly, as explained below) asserts that the cirrhosis was "mild." (Siddiqui Rep. at 30.)

Based on all the above data, it is clear that Mr. Roberts had undiagnosed/unrecognized cirrhosis several years prior to his HCC diagnosis, likely as early as November 2015, when an elevated Fib-4 is first confirmed in his records, and certainly by the time of his April 2016 CT scan as noted above. For any qualified hepatologist, in accordance with multiple society guideline recommendations,[20, 43, 44] in a patient with long-standing MASLD/MASH, Fib-4 >2.67, nodular liver contour on imaging, splenomegaly, recanalized umbilical vein, and thrombocytopenia, no further testing is necessary for confirmation of cirrhosis.[19] In short, the medical evidence demonstrates that Mr. Roberts had cirrhosis—the most significant risk factor for HCC—by April 2016 *at the latest* (when cirrhosis was confirmed on CT imaging). Thus, Mr. Roberts' cirrhosis pre-dated his alleged exposure to NDMA-contaminated valsartan beginning in September 2016, as well as his HCC diagnosis in August 2018.

(2) MASLD/MASH

Background

MASLD (metabolic dysfunction-associated steatotic liver disease) refers to a condition where fat has infiltrated the liver (termed hepatic steatosis) related to excess body weight (i.e., overweight or obesity), and which is commonly associated with additional major metabolic comorbidities, including hypertension, hyperlipidemia, diabetes mellitus, and obstructive sleep apnea.[45, 46] MASH is a histopathologic diagnosis (i.e., technically only confirmed on a liver biopsy) that demonstrates liver inflammation associated with the presence of fat infiltration (called steatohepatitis).[47] In the modern era of practice, most providers do not routinely biopsy patients to formally demonstrate MASH, but rather, MASH is inferred through non-invasive testing of blood markers called transaminases.[19, 48] These include aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are standard components of so-called liver function tests (LFTs). MASLD is typically diagnosed through demonstration of liver steatosis on imaging (e.g., ultrasound), elevation of transaminases, and ruling out competing explanations of steatosis (e.g., heavy alcohol use) and elevated transaminases (e.g., hepatitis C virus, hepatitis B virus, autoimmune hepatitis,

etc.).[19, 48] As stated above, there has been a broad nomenclature shift in the classification of steatotic liver diseases as of December 2023. Among other changes, the term non-alcoholic fatty liver disease (NAFLD) has been replaced with MASLD, and NASH (non-alcoholic steatohepatitis) has been replaced with MASH. This change was made in part to acknowledge a broad spectrum of steatotic liver disease, which includes MASLD, ALD, and the new etiology of liver disease MetALD (overlap of MASLD and ALD). Patients with MASLD, in addition to having steatosis on imaging and no significant alcohol use, must have at least one "cardiometabolic risk factor," including, for example, type 2 diabetes mellitus, overweight or obesity, hypertension, hypertriglyceridemia, or dyslipidemia.[49]

With respect to HCC, it is important to highlight that MASLD and MASH increase the risk of HCC in two ways: (1) through the development of cirrhosis (i.e., MASLD/MASH causes cirrhosis, which in turn dramatically increases the risk of HCC), and (2) as an independent risk factor, a point that has become increasingly well-recognized in the medical community over the past decade. The latter is demonstrated through the observation that many patients with MASLD/MASH develop HCC in the absence of cirrhosis, including in large population-level studies.[50-52] For instance, in a national Swedish study of patients diagnosed with HCC from different causes of liver disease, HCC patients with MASLD were significantly less likely to have cirrhosis versus other groups (61% vs. 82%, $p<0.001$).[52] With declining rates of hepatitis C virus-related liver disease and rising rates of obesity in the United States, MASLD has also become the fastest-growing cause of HCC in liver transplantation candidates.[53] Moreover, up to one third of MASLD-related HCC occurs in the absence of cirrhosis,[50] again demonstrating that cirrhosis is not a requirement to develop HCC in patients with long-standing MASLD and significant hepatic fibrosis. The plaintiff's expert's own report demonstrates that this is the case. As Dr. Siddiqui concedes, "***[a]pproximately 13% of patients diagnosed with HCC without a background of cirrhosis were noted to have NAFLD***. NAFLD is the most common liver disease in the world and has been increasingly linked to liver cancer, especially in individuals with progression to NASH." (Siddiqui Rep. at 21 (emphasis added).) Multiple studies suggest that the increased risk attributable to MASLD/MASH itself is approximately 1.8-fold higher as compared to the general population.[54-56] Results from these studies and others have led some major national societies (e.g., the American Gastroenterological Association) to advocate for routine HCC screening in patients with MASLD and concern for advanced fibrosis (i.e., Fib-4 >2.67), even if cirrhosis is not present.[57]

Relevance of MASLD/MASH to Mr. Roberts' Case

Mr. Roberts had long-standing MASLD and MASH prior to his HCC diagnosis. In addition to having multiple cardiometabolic risk factors (obesity, diabetes, hypertension), he had known hepatic steatosis as identified on numerous imaging studies across a wide span of time (e.g., 9/2009 and 6/23/2016 ultrasounds), as well as elevated transaminases "all of his life" (per Dr. Ives documentation). A chronic liver disease work-up performed by Dr. Hooks in July 2018 was negative for competing etiologies of liver disease (e.g., no evidence of hepatitis B virus, hereditary hemochromatosis, alpha-1 antitrypsin deficiency, Wilson

disease, autoimmune liver disease, etc.), and while there is an isolated reference to "significant alcohol intake" in Dr. Bullard's 10/26/2012 note, all other notes state that Mr. Roberts did not have significant alcohol use. This leaves MASLD/MASH as the etiology of liver disease; this is consistently reflected in the problem list of his treating providers throughout his medical history, generally referred to as "NASH" consistent with the former nomenclature. Thus, MASLD/MASH is the underlying cause of liver disease that led to cirrhosis and HCC in Mr. Roberts' case. Importantly, however, given that MASLD/MASH is a significant independent risk factor for HCC as noted above, even if Mr. Roberts hypothetically never had a diagnosis of cirrhosis, his long-standing MASLD/MASH would be a sufficient medical explanation for developing HCC.

(3) Obesity

Obesity is defined as a body mass index (BMI) >30, with class I obesity defined as BMI 30-34.9, class II obesity as 35-39.9, and class III obesity as 40 and above.[58] Similar to other metabolic comorbidities, obesity is strongly co-associated with MASLD/MASH and thus can contribute to HCC risk as mediated through development of cirrhosis. However, numerous studies have also demonstrated that obesity is also an independent risk factor for HCC.[59-62] For instance, in a meta-analysis of 28 prospective studies including over 8 million patients, increasing BMI was associated with progressively higher risks of HCC.[63] Relative to normal weight individuals, those with BMI >25 had a 1.36-fold increased hazard of HCC, those with BMI >30 a 1.77-fold increased hazard of HCC, and those with BMI >35 had a 3.08-fold increased hazard of HCC. Importantly, models from the studies included in this meta-analysis were adjusted for a broad range of demographics, metabolic, and liver-related comorbidities, isolating the independent effect of obesity on HCC. Additionally, in general population studies, obesity has been associated with a 1.5- to 4.5-fold increased risk of HCC.[64-67] For instance, in two prospective, nationwide cohorts, overweight and obesity classes were significantly associated with incident HCC relative to normal weight individuals, with models adjusted for key demographic, lifestyle behavior, and metabolic comorbidity variables. There was a dose-response effect such that patients with BMI ≥35 had a 2.69-fold increased hazard of HCC, those with BMI 30-34.9 had a 1.80-fold increased hazard, and those with BMI 25-29.9 had a 1.30-fold increased hazard (p for trend = 0.004).[65] Moreover, adults experiencing weight gain over time had progressively increasing risk of HCC. Finally, in a recent study by Kanwal, et al., overweight/obese patients had a 79% adjusted increased risk of HCC relative to normal weight patients.[23]

Mr. Roberts consistently had a BMI in the range of class II obesity (BMI >35) long before his HCC diagnosis, and presumably had significant excess body weight since at least early adulthood given that, as above, he had elevated liver tests "all of his life." Class II obesity appears to have been formally diagnosed based on the first record where BMI is noted in 5/22/2008, at which time Mr. Roberts' BMI was 38.8. His BMI was 37.16 on 3/17/2011, 37.36 on 3/3/2014, and 39.00 on 7/9/2015, demonstrating that Mr. Roberts was consistently in the range of class II obesity, which would be expected to independently confer an approximate ~3-fold increased risk of HCC relative to a non-obese individual.[63] Only much later in Mr.

Roberts' course did he begin to lose weight, after his diagnoses of decompensated cirrhosis and HCC, which were themselves the primary drivers of weight loss.[68, 69]

(4) Diabetes Type II

Similar to obesity, diabetes mellitus (DM) may impact risk of HCC, both as mediated through MASLD and cirrhosis and as a well-established independent risk factor of HCC. Though the specific point estimates vary in magnitude depending on the study, type 2 diabetes is consistently and strongly associated as an independent risk factor for HCC across a wide body of literature. A meta-analysis of 17 case-control studies demonstrated a 2.31-fold increased risk of HCC in patients with diabetes relative to non-diabetics,[70] a meta-analysis of 28 prospective studies reported a 1.87-fold increased risk of HCC in diabetics versus non-diabetics,[71] and in a cohort of MASLD patients with cirrhosis, diabetes was associated with a 4.2-fold increased hazard of HCC versus non-diabetics.[72] Recent data from our research group also establish that degree of poor blood glucose control is also associated with risk of HCC; for instance, patients with a hemoglobin A1c >7% had a 1.80-fold increased hazard of HCC, and those with an A1c >8% a 2.43-fold increased hazard of HCC, each relative to patients with good blood glucose control.[73]

Mr. Roberts appears to have been initially diagnosed with DM in 6/2007 (more than a decade prior to formal diagnosis of HCC (*see* GRobertsJr-CA-000731)), at which time hemoglobin A1c was determined to be 6.9%. In subsequent notes from Dr. Buckley (e.g., 12/20/2007 (*see* GRobertsJr-CA-000729)), "DM" begins to appear in the impression/plan with associated management. Mr. Roberts was accordingly referred to a Diabetes Center nutritionist/certified diabetes educator for help with lifestyle changes to address this issue (visit date 5/22/2008). (*See* GRobertsJr-CA-000722.) The diagnosis of DM appears to have dropped off Mr. Roberts' problem list for a number of years, until it is again noted in 7/2016 in Dr. Sanders' documentation (more than two years prior to his formal diagnosis of HCC). (*See* GRobertsJr-AMG-000043.) At that time, Mr. Roberts' hemoglobin A1c was 9.5%, demonstrating very poor control of blood sugars. (*See* GRobertsJr-AMG-000047.) This placed him in a higher tier of risk for HCC as per the data cited above, with an approximate 2.4-fold increased HCC risk attributable to his diabetes.[73]

(b) Mr. Roberts' Valsartan Use Is Not An Established Risk Factor For HCC.

There is no established scientific basis upon which to conclude that Mr. Roberts' valsartan use was a possible cause of his HCC.

First, neither NDMA exposure nor valsartan use is an established risk factor for HCC. In reviewing the three major national and international hepatology society guidelines for HCC, including from the AASLD,[4] EASL,[74] and the Asian Pacific Association for the Study of the Liver (APASL),[75] none recognizes NDMA or valsartan as a risk factor for HCC, nor do they recommend intensified cancer screening in patients with these exposures. Risk factors that are noted in these guidelines include cirrhosis as the strongest and most relevant risk factor,

MASLD/MASH, obesity, diabetes, chronic hepatitis B virus infection, chronic hepatitis C virus infection, heavy alcohol use, and smoking,[4] many of which are directly relevant to Mr. Roberts' case.

Second, Dr. Siddiqui's suggestion that NDMA exposure has been clearly linked to liver cancer in humans (*see* Siddiqui Rep. at 25) is incorrect. Dr. Siddiqui cites a World Health Organization document from 2002 that states that it "is considered highly likely that NDMA is carcinogenic to humans" and an International Agency for Research on Cancer monograph that classifies NDMA as a "probable human carcinogen." It is important to highlight that a "probable" carcinogen is not a "confirmed" carcinogen in humans; nor is it proof of causation in humans. In evaluating the WHO report, all of the data presented to support the "likely carcinogenic" nature of NDMA to humans in fact come from animal (primarily rodent) studies. Interestingly, many of these rodent studies suggest that a variety of different cancer types may be associated with NDMA exposure, including "nasal, hepatic, pulmonary, and renal tumours," among others. The only human studies that are referenced in the WHO report as pertaining to cancer come from four case-control studies and a population-based cohort study, all from the 1990s. As noted in the report, "[i]n three of four case-control studies, there was a positive relationship with evidence of exposure-response for the intake of NDMA and gastric cancer" and "[i]n a population-based cohort study ... the relative risk of colorectal cancer was increased for the group having the highest intake of NDMA." Liver cancer is not addressed in these studies. Likewise, when discussing the biologic plausibility of NDMA's liver-related carcinogenic potential in humans, Dr. Siddiqui cites only animal studies.[76] Additionally, although she states that "[i]n animal studies, NDMA has been shown specifically to cause a high incidence rate of hepatocellular carcinoma," in the study she cites (Peto, et al.), there was actually a larger number of bile duct cancers (cholangiocarcinoma, a different type of liver cancer) than liver cell cancers (HCC) in all NDMA-treated rodents (443 vs. 417). Another rodent study similarly found an increased risk of bile duct cancers in NDMA-exposed hamsters, particularly in the context of Helicobacter pylori infection, again drawing into question the specific link between NDMA and HCC (because both bile duct cancers and HCC are "liver cancers").[77]

While there is basic science evidence linking NDMA to "liver cancer" in animal studies, these data cannot be assumed to extrapolate directly to humans. Indeed, there are many famous examples of concerning findings in rodent studies that ultimately were not found to translate to humans. For instance, rodent studies demonstrated that saccharin exposure resulted in bladder cancer, raising significant concern regarding human exposure through artificial sweeteners. Early research stated that saccharin was "most likely carcinogenic in human beings."[78] However, these findings were not demonstrated in long-term human studies and ultimately, the American Cancer Society reported that there was no clear evidence that saccharin could cause cancer in humans.[79] Similar conclusions emerged from toxicology reviews and accumulated epidemiologic data.[80] This disconnect is often referred to as the "translation gap" and typically results from key differences in metabolic pathways, exposure levels, and disease biology between animal models and humans.[81]

Third, Dr. Siddiqui's statement that epidemiological literature establishes that NDMA-contaminated valsartan use is a risk factor for HCC is also incorrect. She discussed three epidemiologic studies that have studied this potential association but provides only a superficial interpretation of each when drawing her conclusions. She frames these studies as having a "test group of participants who consumed NDMA-contaminated valsartan and compare[d them] to a control group of participants who consumed valsartan that was not contaminated with NDMA." This is a false framing of the studies, as it implies that patients were subjected to a randomized intervention, when in fact all studies were retrospective cohort studies attempting to compare patients who were exposed to contaminated valsartan in the course of routine care versus those who were not exposed to contaminated valsartan. This subtle point is important to highlight because retrospective observational studies, in particular pharmacoepidemiology studies, are subject to myriad biases and must be carefully scrutinized. Dr. Siddiqui states that the Gomm et al. and Mansouri et al. studies "found a statistically significant increased risk of liver cancer for participants who consumed valsartan contaminated with NDMA" and that "while these studies had multiple limitations … multiple valsartan epidemiological studies still detected an increased risk of liver cancer." (Siddiqui Rep. at 26.) The observation that two studies both identified a similar association does not preclude the possibility that both studies have significant methodological flaws.

Gomm et al.

In the Gomm et al. study, which involved a large German cohort, the authors reported a significant association between NDMA-contaminated valsartan exposure and liver cancer with a small effect size (HR 1.16, 95% CI 1.03-1.31), but no association with cancer risk overall.[82] There are several issues with this study that undermine its reliability. First, the observed effect size is extremely small and lies within a range often attenuated or nullified by unmeasured confounding.

Second, there are major concerns regarding exposure and outcome misclassification. The authors assume subjects had ongoing NDMA exposure from the time of a single contaminated prescription fill, without accounting for real-world issues such as medication discontinuation, switching to an uncontaminated product, or non-adherence with medical directions—each of which could significantly bias exposure classification. Moreover, the authors could not measure the actual NDMA content in the valsartan pills taken by subjects. Instead, exposure was categorized based on the *estimated likelihood* of contamination at the batch level (i.e., "possibly" or "probably" contaminated), which may not reflect true individual-level exposure. Regarding outcome misclassification, all cancers were classified using broad groupings of ICD-10 diagnosis codes, which in the case of liver cancer does not isolate HCC. Most notably, in addition to HCC, the ICD-10 "C22" grouping includes bile duct cancers (cholangiocarcinomas), as well as hepatoblastomas, angiosarcomas, and other malignant neoplasms in the liver. This is concerning, especially in light of the animal data above identifying predominant bile duct cancers with NDMA exposure.

Third, after finding no significant association between NDMA exposure and overall cancer risk in the primary model, the authors examined multiple individual cancer sites without adjustment for multiple comparisons. Because the possibility of chance findings (false positives) increases as the number of tested endpoints increases, the authors' methods increased the likelihood of identifying a false positive statistical association.

Fourth, with respect to the association identified with "liver cancer," there was no dose-response effect observed. This is because the associations identified at the highest rate of exposure (measured as a defined daily dose or "DDD") were lower than those in subjects who received the lowest rate of exposure, which is an important data point that cuts against a finding of causality, especially in light of Dr. Siddiqui's claim that a dose-response effect is expected based on animal studies. (Siddiqui Rep. at 25.)

Fifth, while the authors adjusted for several comorbidities (e.g., diabetes, heart failure, chronic obstructive pulmonary disease, alcohol-related diseases) and included the Charlson comorbidity index, several major confounders relevant to HCC risk—such as BMI, baseline liver disease, and hepatic fibrosis or cirrhosis—were not accounted for. These omissions are likely to bias the association. Importantly, patients in the NDMA-exposed group had higher prevalence of diabetes, heart failure, polypharmacy, and high CCI scores, as well as a greater proportion of prevalent valsartan users. These characteristics suggest a higher burden of metabolic comorbidities and probable overrepresentation of MASLD/MASH and hepatic fibrosis in the exposed group, which could independently elevate liver cancer risk, irrespective of NDMA exposure. Finally, the absence of observed associations with cancers previously linked to NDMA in animal models (e.g., renal, lung, colorectal cancers) raises questions about the translatability of these preclinical findings to human populations—or, alternatively, highlights the cumulative impact of exposure misclassification and residual confounding in this study.

Mansouri et al.

In the Mansouri et al. study, which involved a large national database of French adults, the authors identified a significant association between NDMA-contaminated valsartan exposure and both liver cancer (HR 1.12, 95% CI 1.04-1.22) and melanoma (HR 1.10, 95% CI 1.03-1.18) but no association with overall risk of cancer.[83] While this study does have some methodologic improvements over the Gomm et al. study, including use of inverse probability treatment weighting (IPTW) and appropriate handling of multiple comparisons, there are again major limitations in this study. First, the authors identify a very small effect size (HR 1.12) that may be nullified by unmeasured confounding, and once again, there was no dose-response observed between NDMA-contaminated valsartan and incident liver cancer (i.e., HR 1.14, 95% CI 1.02-1.27 in those with ≤80mg/day and HR 0.99, 95% CI 0.71-1.37 in those with >160mg/day).

Second, there is similar concern regarding exposure and outcomes misclassification. In this case, NDMA-contaminated valsartan was identified based on manufacturer disclosure

rather than batch-level data, and while the authors attempted to account for exposure changes over time, patients were still assumed to be exposed for up to one year after switching medications. This does not account for non-adherence, precise switching patterns, or actual NDMA content of dispensed tablets, introducing considerable potential for exposure misclassification. The outcomes classification is also problematic in the Mansouri et al. study because "liver cancer" is adjudicated based on the C22 grouping of ICD-10 codes; this again does not uniquely identify HCC.

Third, while IPTW was used to balance important confounders, including "obesity" and "hepatic cirrhosis or fibrosis or liver failure," the definitions of these variables lack clinical precision and may result in misclassification. Both are based on ICD-10 codes: the obesity codes (E66) lump together all patients with overweight or any obesity class, failing to differentiate between degrees of risk. Further, the inclusion of bariatric surgery as a proxy for obesity is problematic, as patients who have undergone such procedures may no longer be obese. Similarly, the liver disease codes used (R18, I85, K70, K71, K72, K74) cover a broad spectrum of conditions—from mild chronic liver disease to compensated and decompensated cirrhosis—without distinguishing severity. As a result, these crude classifications likely leave important residual confounding that could bias the observed associations.

Fourth, the authors reported that the associations between NDMA-contaminated valsartan and liver cancer were by far the strongest in individuals from the poorest or most deprived social classes (HR 1.35, 95% CI 1.12-1.63). This finding is suggestive of major issues with confounding in the primary analysis because social deprivation is closely linked to numerous liver cancer risk factors—such as obesity, alcohol use, and MASLD/MASH—that are poorly captured or entirely unmeasured in this dataset. The fact that the effect size increases in this subgroup suggests that the observed association in the overall population may be at least partly attributable to these unmeasured or inadequately measured confounders, rather than a true carcinogenic effect of NDMA in humans.

Finally, the finding of increased association between NDMA-contaminated valsartan and malignant melanoma is unusual given that this was not observed in the Gomm et al. study; nor were melanomas reported to be associated in animal studies related to NDMA. This raises concerns about external validation, false positive association, and/or biased effect size estimates, in addition to prior points about lack of translation between animal models and human studies.

Pottegård et al.

Pottegård et al. studied a large Danish health registry and did not observe a statistically significant association between NDMA exposure and overall cancer risk (HR 1.09, 95% CI 0.85–1.41); nor did they find significant associations with specific cancer types.[84] Given the absence of an observed signal for liver cancer, I will refrain from a detailed critique. However, the study shares several limitations with other analyses, including exposure

misclassification and potential for residual confounding.[1]

Hidajat, et al.

Dr. Siddiqui also references an occupational health study by Hidajat, et al. that evaluated risks of cancer mortality in a cohort of British factory workers in 1967; this study reported that cumulative exposure to NDMA was associated with all cancers (subhazard ratio [SHR] 2.08, 95% CI 1.96-2.21) and multiple cancer subtypes, including bladder, stomach, leukemia, multiple myeloma, prostate, and liver. Dr. Siddiqui states that "workers in rubber and dye factories who were exposed to higher amounts of NDMA in the industry were more likely to die due to liver cancer than workers who were exposed to lower amounts of NDMA in the factory." (Siddiqui Rep. at 26.) However, this is misleading, and Dr. Siddiqui does not acknowledge major limitations and caveats of the data.

First, this study could not isolate NDMA exposure. Workers in the rubber industry were exposed not only to NDMA, but also to other N-nitrosamines, rubber dust, rubber fumes, benzene, and asbestos, among many others. Benzene in particular has substantial data linking it to liver cancer in humans and, in contrast to NDMA, is a definite human carcinogen as classified by the IARC (IARC Group 1).[85, 86] In the Hidajat et al. study, exposures often co-occurred, making isolation of NDMA's effect virtually impossible.

Second, exposures were classified based on factory departments in 1967 and assumed that workers remained in the same department until retirement, emigration, or death—this is unlikely to be accurate for many workers over a 49-year period, and there are no individual-level data for direct measurement of actual exposures. This is a serious limitation because the NDMA exposure values varied significantly based on job location and task within the factory.

Third, the study assessed only cancer mortality—not cancer incidence—thereby missing non-fatal or earlier-stage cancers. It is possible, for instance, that cancer incidence was similar across exposure tiers, but workers with the highest cumulative exposures to multiple toxins had worse survival and thus higher mortality.

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[1] Jeon et al. is an additional study on use of potentially contaminated valsartan and risk of cancer, but the study did not restrict its analysis to NDMA-contaminated valsartan. The authors of Jeon et al. studied over 150,000 valsartan users between 2002 and 2015 and the risk of cancer in a South Korean population. There was no increased overall risk of cancer when comparing valsartan users to other angiotensin II receptor blocker users (HR 1.00, 95% CI 0.98-1.02), but there was a slight increased association in the hazard of liver cancer (HR 1.09, 95% CI 1.01-1.16). The authors found an inverse dose-response relationship between use of valsartan and cancer. There were a number of important limitations regarding this study, including the inability to sort the NDMA-contaminated valsartan products from the other valsartan products used by study participants. In addition, the authors did not have data on a number of important factors, including physical activity, smoking, or diet of the participants. Further, the authors were not able to adjust for potential confounders such as chronic hepatic viral infections.

Fourth, the study was unable to account for key confounders. There were no data available regarding alcohol use, viral hepatitis infections, obesity and metabolic syndrome, smoking, or comprehensive occupational co-exposures, all of which are associated with risk of liver cancer.

Fifth, as in other studies, the "liver cancer" mortality outcome classification has major limitations. The authors used death certificate data to classify cancer groupings, which generally rely on ICD codes. As noted above, pooled "liver cancer" codes would not differentiate between HCC, bile duct cancers, or other liver cancers, thus greatly limiting the specificity of the outcome attributed to NDMA.

Finally, Dr. Siddiqui's suggestion that this study provides definitive evidence of a link between NDMA and liver cancer is in conflict with the study's associations between NDMA and several other cancers—such as bladder, stomach, leukemia, multiple myeloma, and prostate—which are not identified as NDMA-associated cancers in the other epidemiologic literature she cites. This inconsistency raises further concerns about the validity and specificity of the observed associations.

Across all studies discussed, I also note limitations in external validity. Each was restricted to national European cohorts, and it remains unclear whether any observed associations would replicate in a North American population with distinct dietary, lifestyle, environmental, and cardiometabolic risk profiles.

Dr. Siddiqui concludes her assessment of the relevant literature by claiming "the valsartan epi findings on an increased risk of liver cancer based on ever being exposed to NDMA contaminated valsartan massively underestimate the increased risk of someone who was exposed to the higher levels of NDMA contaminated valsartan, as the results are significantly diluted by those with the lowest exposure levels." (Siddiqui Rep. at 28.) The assertion that low-exposure individuals "diluted" the observed liver cancer risk is unsupported by data. As explained above, none of the valsartan epidemiological studies demonstrated a clear dose-response relationship, and stratified analyses failed to show significantly elevated liver cancer risk at higher exposure levels. Without evidence of a gradient of risk, Dr. Siddiqui's claim is scientifically unfounded.

Finally, Dr. Siddiqui ignores a wealth of scientific evidence demonstrating that ARB medications such as valsartan are in fact associated with a reduced risk of HCC, liver-related complications, and death. For instance, in a national study by Elhence, et al., patients with cirrhosis exposed to renin-angiotensin-aldosterone system (RAAS) inhibiting antihypertensives (ARBs and ACE-inhibitors) had a 31% lower adjusted hazard of liver-related adverse events (LREs, including HCC, transplant, or decompensation) relative to patients exposed to selective beta blockers, and a 33% reduced hazard of LRE or death.[87] In a large Veterans Affairs cohort, our group found that patients with cirrhosis exposed to ARBs/ACE-inhibitors had a lower risk of all-cause mortality (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.61-0.81), and a trend towards reduced risk of HCC that was not

statistically significant (HR 0.83, 95% CI 0.56-1.22) as compared to calcium channel blocker exposure.[88] Importantly, both of these studies utilized comprehensive adjustment of potential confounders using causal inference methodology incorporating inverse probability treatment weighting (IPTW, a means of "mimicking" a randomized-controlled trial) as well active comparison to alternate medications with similar medical indications as ARBs. In a population-based study of non-cirrhotic patients with chronic liver disease, Chen, et al. demonstrated that ARB/ACE-inhibitor exposure was associated with a lower hazard of incident HCC (HR 0.66, 95% CI 0.50-0.86), liver-related mortality (HR 0.77, 95% CI 0.64-0.93), and incident cirrhosis (HR 0.81, 95% CI 0.70-0.94) when compared to patients exposed to calcium channel blockers or thiazide diuretics.[89] Finally, in a meta-analysis of relevant studies, Asgharzadeh, et al. found that ARB/ACE-inhibitor exposure was associated with a ~30% reduced risk of HCC relative to non-exposure (relative risk [RR] 0.704, 95% CI 0.526-0.944). In a subgroup analysis limited to only ARB-exposed patients, the effect size was intensified such that patients had a ~45% reduced risk of HCC (RR 0.545, 95% CI 0.470-0.632).[90] To contextualize these results, there is biological plausibility for ARB medications reducing risk of HCC and liver-related complications. Activation of the renin-angiotensin-aldosterone system (RAAS) induces hepatic fibrosis (liver scarring) through collagen deposition and release of various inflammatory cytokines.[91, 92] Thus, inhibition of the RAAS through ARBs or ACE-inhibitors may prevent or even reverse some degree of hepatic fibrosis. Given the above literature and basic science foundation, it is plausible that Mr. Roberts' prolonged exposure to valsartan in fact had a protective effect on the liver, potentially delaying the onset of his cirrhosis and HCC.

(c) Dr. Siddiqui's Differential Diagnosis—And Resulting Opinions Regarding The Cause Of Mr. Roberts' HCC—Are Scientifically Invalid.

Dr. Siddiqui purports to have based her opinion that Mr. Roberts' use of NDMA-contaminated valsartan was the "only substantial factor in causing his liver cancer" on a methodology known as a "differential diagnosis." According to Dr. Siddiqui, she used this methodology to "rule in" NDMA-contaminated valsartan as the cause of Mr. Roberts' HCC and to "rule out" all other possible causes and contributing factors of his HCC. However, Dr. Siddiqui made incorrect medical and scientific statements and conclusions at both steps of this methodology.

(1) Dr. Siddiqui Lacks a Scientific Basis to Rule in Valsartan Use as a Cause of Mr. Roberts' HCC.

Dr. Siddiqui states: "[i]t is my opinion that NDMA exposure from valsartan was the cause of Mr. Roberts' hepatocellular (liver) cancer" (Siddiqui Rep. at 32), but the relevant science does not meet recognized causality standards, as demonstrated through an evaluation of the causality considerations adopted by Sir Austin Bradford Hill.[93, 94]

First, as detailed above, the cited literature **does not demonstrate specificity** between NDMA exposure and risk of HCC, largely because of exposure and outcome misclassification**.**

Second, there is an insufficient number of studies addressing liver cancer incidence in valsartan users to reliably evaluate **consistency**, and to the extent consistency can be evaluated, the reported associations between NDMA and cancers (or lack thereof) vary substantially across studies, and further lack consistency with animal studies.

Third, when associations between NDMA exposure and incident liver cancer are reported (in Gomm et al. and Mansouri et al.), they are **weak associations** that are subject to nullification through residual confounding.

Fourth, studies reporting associations between NDMA-contaminated valsartan and liver cancer **did not demonstrate dose-response**, indicating a lack of biological gradient.

Finally, despite Dr. Siddiqui's assertions to the contrary, **the temporality criterion is highly dubious.** For causation, an exposure must precede an outcome by a sufficient period to plausibly contribute to the development of the disease.

The Hidajat et al. study incorporated a 15-year exposure lag in its analyses, excluding cancer mortality outcomes that occurred within 15 years of the estimated NDMA exposure. This approach was used to account for the expected latency period of cancer development following exposure to carcinogens. Neither the Gomm et al. nor Mansouri et al. study reports median time from exposure to liver cancer diagnosis, but both assumed just a one-year lag period. These one-year lags are very conservative (i.e., latency periods for solid tumors are typically much longer), and it is important to note that in Mansouri et al., when the lag period was extended to two years in a sensitivity analysis, the adjusted hazard of liver cancer *decreased* (HR 1.10, 95% CI 1.03-1.17). This strongly suggests misclassification/misattribution of early liver cancer cases to NDMA-contaminated valsartan.

While not relevant to a general causation opinion under Bradford Hill, temporality is particularly concerning in this case. There is no direct evidence provided by Dr. Siddiqui to suggest that Mr. Roberts' exposure to NDMA (beginning just 23 months prior to his HCC diagnosis) would provide sufficient exposure and latency to plausibly link the NDMA exposure to his cancer.

Moreover, I must emphasize that **Mr. Roberts did not present with early-stage HCC**. At that time of his diagnosis in 2018, he had multifocal lesions with large tumor size. The largest HCC tumor on his 8/16/2018 MRI was 5.8cm in diameter. As established in a meta-analysis of 20 studies, the average tumor volume doubling time (TVDT) for HCC is 4.6 months, with a 95% CI of 3.9 to 5.3 months.[95] We can use these data to estimate historic tumor sizes and

likely time of incident HCC using average, aggressive growth, and slow growth scenarios. Assuming a spherical shape for an HCC tumor, the volume of the sphere is given by

$$V = \frac{1}{6} * \pi * d^3$$

where *V* is volume and *d* is diameter. Solving for diameter, we would have:

$$d = \left(\frac{6 * V}{\pi}\right)^{1/3}$$

We can use this relationship to "back-calculate" expected tumor diameter prior to the 8/16/2018 MRI and therefore impute expected tumor size (if present) at the time of Mr. Roberts' first alleged exposure to NDMA-contaminated valsartan. I have summarized these relationships below for each TVDT assumption (shaded cells indicate time periods prior to Mr. Roberts' first alleged NDMA-contaminated valsartan exposure):

Tumor Volume (cm^3)	Tumor Diameter (cm)	Time Before Detection (average, 4.6 month TVDT)	Time Before Detection (slow growth, 5.3 month TVDT)	Time Before Detection (aggressive growth, 3.9 month TVDT)
102.16	5.80	0.0	0.0	0.0
51.08	4.60	4.6	5.3	3.9
25.54	3.65	9.2	10.6	7.8
12.77	2.90	13.8	15.9	11.7
6.385	2.30	18.4	21.2	15.6
3.1925	1.83	23.0	26.5	19.5
1.59625	1.45	27.6	31.8	23.4
0.798125	1.15	32.3	37.1	27.3

It is clear in evaluating these data that across all scenarios, including the most conservative scenario assuming aggressive tumor replication and growth, **Mr. Roberts almost certainly had undiagnosed HCC at the time of his first exposure to allegedly NDMA-contaminated valsartan in September 2016**. These projections are consistent with the expert report authored by Dr. Victoria Chernyak (radiologist), who reviewed Mr. Roberts' 4/8/2016 CT of the abdomen and noted three LR-3 lesions (intermediate probability of malignancy), measuring 0.6cm (segment VII), 0.5cm (segment V/VIII), and 0.5cm (segment VI). (Chernyak Rep. at 5 & Exhibit B.) Of critical importance is Dr. Chernyak's observation that the segment V/VIII lesion is in the same location as one of the LR-5 lesions later confirmed on the 8/2018 MRI. (Chernyak Rep. at 6 & Exhibit D.) It therefore cannot be ruled out that this LR-3 lesion represented HCC, which subsequently grew to become the LR-5 lesion that was identified on the later MRI. All of the above points clearly demonstrate that the temporality criterion for causality between NDMA-contaminated valsartan and HCC in this case is not met.

Second, Dr. Siddiqui also claims that "Mr. Roberts' exposure to NDMA-contaminated valsartan promoted his cancer to be more aggressive and progress faster, which made his cancer harder to treat and limited his treatment options." (Siddiqui Rep. at 29.) I am unable to find any scientific evidence to support Dr. Siddiqui's assertion that valsartan increases the aggressiveness of HCC tumors, and she does not provide any citations to support this claim. Further, her assertion that Mr. Roberts' cancer was "harder to treat" with "limited… treatment options" due to NDMA is entirely unsubstantiated. As discussed above, Mr. Roberts' HCC was treated appropriately based on his BCLC stage, and in accordance with guideline recommendations, initially with locoregional therapies (i.e., TACE, SBRT) and then with systemic therapies (i.e., Lenvatinib, nivolumab).[4, 7] Moreover, Dr. Siddiqui's statements in this regard are not supported by any of the treating physicians who managed Mr. Roberts' HCC, none of whom mentioned concerns about unusual aggressiveness of his HCC or any concerns related to NDMA exposure.

Finally, Dr. Siddiqui's backup position that Mr. Roberts' use of NDMA-containing valsartan caused or contributed to Mr. Roberts' cirrhosis, which in turn caused his HCC, is also contrary to the record in this case and unsupported by the scientific evidence. In her report, Dr. Siddiqui asserts that NDMA exposure is a potential cause of cirrhosis, stating that: "like NASH, alcohol can indirectly cause HCC by causing cirrhosis (NDMA can also cause cirrhosis)" (Siddiqui Rep. at 21) and that "[c]irrhosis is caused by chronic liver damage due to a wide variety of potential causes, such as … NDMA exposure" (*id*. at 21). This theory of indirect causation is scientifically invalid. First, Dr. Siddiqui does not provide any citations to support the claim that NDMA causes cirrhosis in humans. Second, a search of the scientific literature and reading of major hepatology society guidelines did not identify any high-quality data in human subjects demonstrating that NDMA causes cirrhosis. Finally, even assuming there were evidence that NDMA exposure could cause cirrhosis in humans (which neither Dr. Siddiqui nor I have identified), it could not explain the development of cirrhosis in the case of Mr. Roberts because he had cirrhosis prior to his first alleged exposure to NDMA-contaminated valsartan, as detailed above. As a result, NDMA exposure could not have caused Mr. Roberts' cirrhosis.

(2) Dr. Siddiqui Lacks a Scientific Basis Rule Out Mr. Roberts' Established Risk Factors for HCC as Causes.

First, Dr. Siddiqui does not have a scientific basis to rule out cirrhosis as a cause of Mr. Roberts' cancer. In her differential diagnosis, Dr. Siddiqui asserts that she "ruled out cirrhosis as the cause of Mr. Roberts' liver cancer" because Mr. Roberts had "incredibly mild, the earliest stages of cirrhosis" and "Mr. Roberts' cirrhosis was incredibly mild in 2016." (Siddiqui Rep. at 30.) In the hepatology community, however, there is no concept of "mild cirrhosis." As detailed previously, scarring in the liver is generally staged from F0 to F4, where F4 fibrosis defines the presence of cirrhosis. While it is true that cirrhosis itself can have varying degrees of severity (e.g., compensated or decompensated), the dramatically increased risk of HCC is inherent to the state of cirrhosis itself, regardless of

severity. For this reason, all major hepatology societies recommend routine HCC surveillance for all patients with cirrhosis, regardless of severity, provided the patient is not already at end-of-life care.[4, 74] Dr. Siddiqui herself acknowledges that many "NASH patients go on to develop cirrhosis, which is a major risk factor for HCC…" and that "cirrhosis is one of the most significant risk factors for liver cancer." (Siddiqui Rep. at 21.) Thus, Dr. Siddiqui's insistence that Mr. Roberts had "mild cirrhosis" in April 2016 or August 2018, and that this somehow mitigated or nullified his risk of HCC from cirrhosis, is unsupported by well-established medical science.

Relatedly, Dr. Siddiqui states: "Dr. White's [Mr. Roberts' hepatologist] note on August 22, 2018, contemporaneous with Mr. Roberts' liver cancer diagnosis, that Mr. Roberts had 'undergone extensive work up for cirrhosis' and that the 'work up for cirrhosis is essentially negative.' Dr. White also noted Mr. Roberts had 'no history of confusion, ascites, LE swelling, jaundice, pruritic, hematemesis, or melena', which are symptoms one would see in an individual with severe cirrhosis or liver failure.'" (*Id.* at 30.) Dr. Siddiqui uses these statements by Dr. White to support her aforementioned position that Mr. Roberts' cirrhosis was "so mild" that she scientifically "ruled out cirrhosis as the cause of … liver cancer." (*Id.*)

This statement is based on a misunderstanding of the clinical relevance of Dr. White's notes. When Dr. White states that a "work up for cirrhosis is essentially negative," this is common phrasing to indicate that serologic testing did not identify any specific cause of chronic liver disease, such as hepatitis B virus, hepatitis C virus, autoimmune hepatitis, or hereditary hemochromatosis, among others. There is no blood test to diagnose MASLD, and thus the 'negative work-up' does not encompass this diagnosis. As noted previously, MASLD is generally diagnosed by ruling out other chronic liver diseases while demonstrating steatosis in the liver in patients with cardiometabolic risk factors.

Dr. White's statements that there was no confusion, ascites, jaundice, or hematemesis are indications that Mr. Roberts did not have *decompensated* cirrhosis at that time. These statements do not mean that cirrhosis was not present, or that it was "mild." Through this history of present illness, Dr. White is communicating that Mr. Roberts had compensated cirrhosis related to MASLD, which he makes explicit in the assessment and plan portion of the notes that refer to Mr. Roberts as a patient with "NASH cirrhosis complicated by HCC." Further, Dr. Siddiqui fails to acknowledge the fact that all clinicians who provided care for Mr. Roberts related to his HCC stated directly or indirectly that NASH/MASH cirrhosis was the underlying condition that led to Mr. Roberts' developing HCC, as highlighted in the review of Mr. Roberts' medical records, above.

Dr. Siddiqui's assertion that Mr. Roberts' "MELD score of 8 at the time of liver cancer diagnosis further supports that Mr. Roberts' cirrhosis was incredibly mild in 2016" (*id.*) is also scientifically unfounded. While the Model for End-Stage Liver Disease (MELD) is strongly predictive of transplant waitlist mortality through 90 days (and thus, MELD-related scores are used to prioritize patients for liver transplantation), it is not an instrument to comprehensively summarize severity of liver disease or risk of short-term death in all

patients with cirrhosis. In my substantial experience, many patients with cirrhosis and low MELD scores are highly symptomatic from their liver disease. In addition, the scientific literature demonstrates that a high proportion of patients with cirrhosis who are diagnosed with HCC have relatively low MELD scores. For instance, Tang et al. found that the median MELD-sodium (MELD-Na) at the time of HCC diagnosis in a cirrhosis cohort was 9.7 (interquartile range 7.5 to 13.9).[96] In addition, data from a large national Veterans Affairs cohort published by my research group demonstrate that patients with cirrhosis and HCC had a median MELD score at liver transplantation of 9 (interquartile range 8-12).[97] Across the national transplantation registry from the United Network for Organ Sharing (UNOS), our group has demonstrated that the median laboratory MELD-Na at the time of transplant waitlisting in patients with HCC is 11 (interquartile range 8-15), and at the time of transplant is between 11 and 12.[98, 99] In fact, because many patients with cirrhosis and HCC have low MELD-Na scores, there is a national transplant policy in place to help increase transplantation priority in these patients (called a "standardized exception" pathway).[8] As a result, there is no legitimate scientific basis to assert that a low MELD score in a patient with cirrhosis suggests that a patient's cirrhosis is "mild" or unlikely to cause HCC.

Dr. Siddiqui also dismisses cirrhosis as a cause of Mr. Roberts' HCC based on the belief that "from the time cirrhosis is first diagnosed, it takes approximately 7-10 years before increased rates of HCC are observed." (Siddiqui Rep. at 22.) There are a number of problems with this assertion. First, Dr. Siddiqui cites Johnson, et al. for this claim, but that study does not support her conclusion. Johnson, et al. noted a median time of 7 years between advanced fibrosis/cirrhosis and HCC among patients diagnosed with HCC in a very specific cohort of patients—those with hepatitis C virus (HCV) who were treated with direct-acting antiviral therapy and cured of HCV. This is a group of patients who have had their primary etiology of liver disease removed, and yet are known to have persistent elevated risk of HCC, even in the absence of cirrhosis. These statistics simply do not apply to patients, like Mr. Roberts, who have MASLD/MASH and cirrhosis. Additionally, Dr. Siddiqui's presentation of the median time from advanced fibrosis/cirrhosis to HCC as reflecting a fixed biologic latency is misleading, as it ignores the underlying variability in disease progression. Some patients develop HCC much earlier, and many are diagnosed at the same time that cirrhosis is first identified.

Dr. Siddiqui's claim is also contradicted by her prior sentence, which states that "the annual incidence of HCC in patients with *diagnosed* cirrhosis is 2-4%." (Siddiqui Rep. at 22). As stated above, large-scale data demonstrate that patients without cirrhosis have extremely low rates of HCC, and the risk dramatically increases when cirrhosis is present. Moreover, major societies would not recommend initiating HCC surveillance protocols at the time of cirrhosis diagnosis if the increased risk of HCC did not begin for 7-10 years. Finally, this claim is contradicted by the data demonstrating that many patients with MASLD/MASH are diagnosed with HCC **even in the absence of cirrhosis**. Thus, the increased risk of HCC is clearly present at any point where cirrhosis is present, as well as in states of advanced fibrosis but without cirrhosis in patients with MASLD/MASH. This is important to highlight, as Mr. Roberts' presentation of being definitively diagnosed with HCC and cirrhosis at the

same time in August 2018 (for clarity it is my view that cirrhosis was clearly present years prior) is entirely consistent with expectations from medical science and literature cited above.

Further, Dr. Siddiqui's attempt to rule out Mr. Roberts' cirrhosis as a cause of his HCC is contrary to the scientific evidence outlined above that: (1) cirrhosis is the strongest and best-established risk factor for HCC; (2) Mr. Roberts had cirrhosis at the time of HCC diagnosis in August 2018, and (3) Mr. Roberts had confirmed cirrhosis several years prior to his formal HCC diagnosis and prior to exposure to NDMA-contaminated valsartan. As further explained above, estimates from multiple large studies demonstrate that cirrhosis confers an approximate 30- to 45-fold increased risk of HCC,[1, 2] which dwarfs any potential effect size that Dr. Siddiqui would attribute to NDMA-contaminated valsartan.

Second, Dr. Siddiqui also lacks a scientific basis to rule out MASLD/MASH as an independent cause of Mr. Roberts' HCC.

In her differential diagnosis, Dr. Siddiqui states that she considered "Mr. Roberts' diabetes, NASH, and obesity together, because when all three are present it can be considered part of a metabolic syndrome that can cause … inflammation … that can eventually lead to cirrhosis." (Siddiqui Rep. at 29.) While I agree that these comorbidities are interrelated and frequently co-present in patients, the available evidence supports the conclusion that **NASH, obesity, and diabetes each have additional independent contributions to HCC risk**. As explained above, in well-adjusted analyses and in studies restricted to patients with MASLD, there are clear incremental increases in HCC risk among individuals with higher obesity classes and in those with diabetes.[32, 63, 65, 70, 72, 73] If all three of these conditions simply captured an overlapping risk, these additive effects on HCC risk would not be observed. Thus, in my view, it is inappropriate and overly simplistic for Dr. Siddiqui to group these important risk factors together as a means of later dismissing them by purportedly "rul[ing] out cirrhosis as the cause of Mr. Roberts' liver cancer." (Siddiqui Rep. at 30.)

Importantly, Dr. Siddiqui also ignores the fact that many patients with MASLD/MASH may develop HCC in the absence of cirrhosis, a point which she herself acknowledges in her discussion of risk factors: "Approximately 13% of patients diagnosed with HCC without a background of cirrhosis were noted to have NAFLD." (Siddiqui Rep. at 21.) Because Dr. Siddiqui admits that HCC can develop in the setting of non-cirrhotic NAFLD/MAFLD, there is no legitimate scientific basis for her to dismiss NASH/MASH as a cause of HCC by purportedly ruling out cirrhosis as a cause.

Third, Dr. Siddiqui lacks scientific basis to rule out Mr. Roberts' other independent risk factors for HCC, including obesity and type 2 diabetes mellitus.

Regarding obesity, Dr. Siddiqui acknowledges that obesity may be associated with HCC as mediated through MASLD and cirrhosis, a point with which I agree. However, Dr. Siddiqui is dismissive of any independent effect that obesity may have on HCC risk, and uses a flawed

understanding of population-level risk data to reach this conclusion. According to Dr. Siddiqui, "the incidence rate of HCC for males was 5.0 per 100,000 persons. Approximately 40% of the US population are obese, but only 0.005% develop liver cancer. Therefore, obesity itself is not a significant risk factor for liver cancer." (Siddiqui Rep. at 22.) This statement improperly conflates population prevalence with individual risk. The claim that "40% of people are obese but only 0.005% develop liver cancer, therefore obesity is not a significant risk factor for liver cancer" is akin to saying "because most smokers do not develop lung cancer, smoking is therefore not a significant risk factor for lung cancer." Risk is not determined by the absolute number of people with a risk factor who develop the condition, but rather by comparing the incidence of the condition in individuals with the risk factor versus those without it.[100-102] Further, Dr. Siddiqui ignores the wide body of literature cited above that demonstrates a statistically significant association between obesity and HCC in adjusted analyses, including increasing gradations of risk with higher obesity classes.[59-63, 65] This includes data demonstrating a ~3-fold increased risk of HCC in individuals with class II obesity (such as Mr. Roberts) relative to non-obese individuals.[63] Thus, Dr. Siddiqui's statement that "Mr. Roberts' increased risk of liver cancer due to obesity would have been negligible, and … [is] best captured based on the degree of his liver cirrhosis" (Siddiqui Rep. at 30) is scientifically unfounded.

Dr. Siddiqui acknowledges that diabetes increases the risk of MASLD, which in turn increases the risk of HCC. (Siddiqui Rep. at 22-23.) We agree on this point. However, as with obesity, Dr. Siddiqui essentially ignores data addressing the independent risk that diabetes may confer with respect to incident HCC. Dr. Siddiqui provides no scientific basis to refute or dispute the relevance of studies (noted above) that demonstrate that type 2 diabetes mellitus is significantly associated with increased HCC risk, and that degree/duration of poor blood sugar control is further associated with this risk.[70-73] This includes studies limited to patients with MASLD, where diabetes conferred a ~4-fold increased risk of HCC relative to non-diabetics.[72]

Dr. Siddiqui also makes the claim that: "Mr. Roberts was not diagnosed with diabetes until November 14, 2016 – after he started taking NDMA contaminated valsartan. Furthermore, it was noted that Mr. Roberts diabetes was well controlled (sic)." (Siddiqui Rep. at 29-30.) These claims are both incorrect. First, Mr. Roberts appears to have been given a diagnosis of diabetes mellitus (DM) in 2007, when Dr. Buckley checked a hemoglobin A1c which returned at 6.9% (diabetes is diagnosed when a hemoglobin A1c is ≥6.5%).[103] (*See* GRobertsJr-CA-000731.) Dr. Buckley's notes then listed DM in the impression, along with associated management plans. (*See* GRobertsJr-CA-000729.) Dr. Buckley referred Mr. Roberts to a nutritionist/certified diabetes educator at the Thomas Hospital Diabetes Center, where he was seen on 5/22/2008. (*See* GRobertsJr-CA-000722.) Mr. Roberts' DM then dropped off his problem list until it was noted and discussed by Dr. Sanders in 7/2016, at which time his hemoglobin A1c was 9.5%. (*See* GRobertsJr-AMG-000043 and GRobertsJr-AMG-000047.) Second, Dr. Siddiqui is incorrect to imply that Mr. Roberts' diabetes was uniformly "well controlled." The American Diabetes Association recommends a target A1c <7.0% as demonstration of "good control."[104] While Mr. Roberts would later achieve "good

control" of diabetes through initiation of multiple medications to manage his diabetes, he was a poorly-controlled diabetic at the time of his hemoglobin A1c check with Dr. Sanders in 7/2016.

In short, Dr. Siddiqui's differential diagnosis is also significantly flawed because she fails to provide a valid scientific basis to rule out both obesity and diabetes as independent causes of Mr. Roberts' HCC. Based on the relevant literature, Mr. Roberts had an approximate ~3-fold risk of HCC attributed to his degree of long-standing obesity, and an approximate ~4-fold increased risk of HCC attributed to his diabetes.

(3) Dr. Siddiqui Lacks Medical and Scientific Credibility to Serve as an Expert Witness in this Case.

A number of other statements and claims made by Dr. Siddiqui in her report severely undermine the credibility of her scientific opinions related to HCC, its development, and its potential causes.

First, Dr. Siddiqui states that "NAFLD mostly occurs in the setting of metabolic syndrome-associated steatotic liver disease (MASLD)." (Siddiqui Rep. at 21.) This statement demonstrates a fundamental misunderstanding of contemporary science surrounding steatotic liver disease. As noted above, MASLD, which stands for metabolic dysfunction-associated steatotic liver disease, is the updated nomenclature that replaced NAFLD (non-alcoholic fatty liver disease).[49] This is part of a broader conceptualization of steatotic liver diseases (SLDs), which refer to chronic liver diseases characterized by the presence of fat (steatosis) in the liver. Stated plainly, NAFLD does not "mostly occur in the setting of MASLD"—rather, NAFLD is the outdated nomenclature for MASLD. This misstatement suggests that Dr. Siddiqui has an antiquated or incorrect understanding of MASLD and its association with HCC, which is central to her ability to conduct a scientifically-sound differential diagnosis.

Second, Dr. Siddiqui asserts that "MASLD is a cluster of conditions – insulin resistance, hypertension, hypertriglyceridemia, and abdominal obesity." (Siddiqui Rep. at 21.) This is incorrect. As noted above, MASLD is an updated nomenclature term that replaces NAFLD. MASLD is defined very precisely in modern guidance as hepatic steatosis with at least one associated cardiometabolic risk factor and an absence of significant alcohol use.[49] Dr. Siddiqui is conflating MASLD with "metabolic syndrome," which is a related but distinct medical term that refers to a cluster of metabolic abnormalities that increase the risk of cardiovascular disease, type 2 diabetes, and MASLD.[105-107]

Third, in discussing the process of diagnosing HCC, Dr. Siddiqui cites guideline data and a diagnostic pathway (the European Association for the Study of the Liver [EASL] from 2000) that is decades out of date. (Siddiqui Rep. at 19.) As explained above, the LI-RADS criteria are applied to multi-phase cross-sectional imaging in modern practice to non-invasively diagnose HCC lesions, including assessment of lesion size, arterial hyperenhancement,

delayed washout, and peripheral capsule.[6] LI-RADS criteria are not mentioned in Dr. Siddiqui's report, and her imaging-based diagnostic algorithm only notes lesion size (i.e., size of the tumor[s]) and arterial hyperenhancement (a CT/MRI imaging feature where the tumor appears bright after contrast is administrated and passing through the arteries) (Siddiqui Rep. at 20), which is severely outdated and not scientifically valid in modern practice. Further, updated guidelines were made available by the AASLD in 2023, as well as by the EASL in 2024, both of which discuss the LI-RADS criteria as the primary mechanism to diagnose HCC.[4, 74] Dr. Siddiqui's reliance on a diagnostic algorithm that is over 20 years out of date calls into further question the scientific reliability of Dr. Siddiqui's opinions regarding HCC, including its risk factors.

Fourth, Dr. Siddiqui also incorrectly states that Mr. Roberts' pain and suffering related to HCC included the experience of undergoing serial large-volume paracenteses to treat his ascites. (Siddiqui Rep. at 20.) Ascites is one of the cardinal decompensations associated with advanced cirrhosis, and results directly from portal hypertension related to significant scarring in the liver.[108] Mr. Roberts clearly had evidence of portal hypertension at the time of his formal cirrhosis diagnosis on his 8/7/2018 MRI; per Dr. Mark Lockhart, this demonstrated "cirrhotic morphology with surface nodularity… splenomegaly, consistent with portal hypertension." (*See* GRobertsJr-PPR-000106.) It is common for many patients with decompensated cirrhosis to require serial large-volume paracenteses (LVPs) in the absence of HCC, and while it is true that in advanced HCC, patients may develop worsened cirrhosis decompensation and thus worsened ascites,[109] the ascites fundamentally remains a complication of the cirrhosis itself rather than the HCC. For this reason, patients who develop HCC in the absence of cirrhosis generally do not have ascites. Mr. Roberts' own treating gastroenterologist, Dr. Samuel Hooks**,** acknowledged this at his deposition, explaining that Mr. Roberts needed paracentesis "because of underlying cirrhosis," and not the HCC itself and that it is not common for a patient with HCC to need paracentesis. (Hooks Deposition Tr. 78:4-7; 80:6-7.) This medically incorrect statement by Dr. Siddiqui further undermines her opinions related to HCC, its causes, and its effects.

6. Conclusion

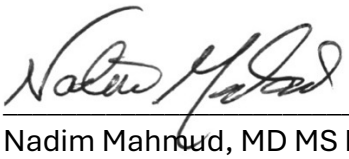
In my expert opinion, **Mr. Gaston Roberts' HCC was the direct result of longstanding MASLD/MASH that resulted in cirrhosis and subsequently HCC**. As noted, there is extensive and well-established literature that is codified in national and international hepatology society guidelines that supports this opinion. Other contributing risk factors for Mr. Roberts' HCC include his prior history of class II obesity and diabetes mellitus.

Further, even if one were to assume Mr. Gaston Roberts did not truly have cirrhosis prior to developing HCC (which, as explained in detail above, is not the case), Mr. Roberts' longstanding MASLD/MASH with hepatic fibrosis itself is a sufficient explanation for incident HCC.

In addition, there is insufficient evidence to causally link NDMA-contaminated valsartan exposure to HCC in humans, as the relevant literature lacks specificity, lacks consistency in its findings, suggests only weak associations with "liver cancer" (if suggested at all), lacks a biologic gradient in its purported effect, and perhaps most importantly to this case, does not come close to approaching the standard of temporality between exposure and outcome. It is therefore unsurprising that no major hepatology society guidelines comment on NDMA exposure as a potential risk factor for HCC, much less recommend any enhanced HCC screening in patients exposed to NDMA-contaminated valsartan. Further, none of Mr. Roberts' numerous and diversely trained treating physicians posited that NDMA-contaminated valsartan could have played a role in his cancer, despite discovery of said contamination nearly two years prior to Mr. Roberts' passing.

In my extensive clinical and research experience, Mr. Roberts' unfortunate case is in fact entirely typical of many HCC cancers that are diagnosed in the United States and does not require invocation of any additional factors to explain his clinical course. Indeed, the clinicians who played a role in managing his HCC either overtly or implicitly stated their understanding that NASH/MASH cirrhosis was the reason that Mr. Roberts unfortunately developed and suffered from HCC.

Signed:



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Date: April 10, 2025

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Exhibit A

University of Pennsylvania
Curriculum Vitae

April 9, 2025

Nadim Mahmud, M.D., M.S., M.P.H., M.S.C.E.

Office Address: Perelman Center for Advanced Medicine
3400 Civic Center Blvd
Philadelphia, PA 19103

Education:

2019	M.S.C.E.	University of Pennsylvania
2013	M.D.	Stanford University School of Medicine
2011	M.P.H.	Columbia Mailman School of Public Health (Biostatistics and Clinical Trial Design)
2008	M.S.	Yale University (Molecular Biophysics and Biochemistry)
2008	B.S.	Yale University (Molecular Biophysics and Biochemistry)

Postgraduate Training and Fellowship Appointments:

2019-2020	Transplant Hepatology Fellowship, Hospital of the University of Pennsylvania, Philadelphia
2016-2019	Gastroenterology Fellowship, Hospital of the University of Pennsylvania, Philadelphia
2014-2016	Residency in Internal Medicine, Brigham and Women's Hospital, Boston
2013-2014	Internship in Internal Medicine, Brigham and Women's Hospital, Boston

Specialty Certification:

2016	ABIM Board Certified in Internal Medicine
2019	ABIM Board Certified in Gastroenterology
2020	ABIM Board Certified in Transplant Hepatology

Licensure: Pennsylvania

Appointments:

2024-present	Associate Program Director for Research & Scholarly Development, Internal Medicine Residency Program, University of Pennsylvania Perelman School of Medicine
2020-present	Assistant Professor of Medicine, Department of Medicine, Hospital of the University of Pennsylvania
2020-present	Assistant Professor of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics (secondary)
2020-present	Assistant Professor of Medicine, Department of Medicine, Michael J. Crescenz Philadelphia Veterans Affairs Medical Center
2020-present	Senior Fellow, Leonard Davis Institute
2020-present	Senior Scholar, Center for Clinical Epidemiology and Biostatistics
2018-2020	Associate Fellow, Leonard Davis Institute
2017-2019	Fellow board member, Pennsylvania Society of Gastroenterology

Major Awards and Honors:

2024	AASLD Emerging Liver Scholar Mentor
2023	Penn DOM Resident Mentoring Award
2023	ASCI Young Physician-Scientist Award
2023	Penn GI Faculty Research Award
2023	AASLD Emerging Liver Scholar Mentor
2022	AASLD Emerging Liver Scholar Mentor
2022	Sandy Norman Epidemiology and Biostatistics Teaching Award
2021	McCabe Foundation Award Recipient
2020	American College of Gastroenterology Junior Faculty Development Award Recipient
2019	Frank Brooks Research Award
2019	Delaware Valley Society of Gastroenterology Research Award
2019	Komarov Research Award
2019	Controversies in Liver Transplantation Debate Champion
2018	Delaware Valley Society of Gastroenterology Research Award
2018	Komarov Research Award
2018	Controversies in Liver Transplantation Oral Presentation Second Prize
2014	Forbes 30 under 30: Social Entrepreneurs
2013	Forbes 30 under 30: Social Entrepreneurs
2013	Digestive Diseases Week Poster of Distinction with Oral Presentation
2012	Iscol Family Program for Leadership Development in Public Service Fellow

2011	Columbia University Teaching Award

Membership in Professional Societies:

2019-present	American Society of Transplantation
2016-present	**American Association for the Study of Liver Diseases** - Member, Journals Publications Committee (2023-2026)
2016-present	American College of Gastroenterology
2016-present	Pennsylvania Society of Gastroenterology
2013-present	American Medical Association
2013-present	American College of Physicians

Editorial Positions:

2023-present	Executive Guest Editor, American Journal of Transplantation
2021-present	Editorial Board member, Liver Transplantation
2021-2022	Associate Editor, Frontiers in Gastroenterology
2023-present	Ad hoc reviewer, New England Journal of Medicine
2019-present	Ad hoc reviewer, Gastroenterology
2019-present	Ad hoc reviewer, British Medical Journal
2018-present	Ad hoc reviewer, Liver International
2018-present	Ad hoc reviewer, Alimentary Pharmacology and Therapeutics
2018-present	Ad hoc reviewer, American Journal of Transplantation
2018-present	Ad hoc reviewer, Journal of Clinical Medicine
2018-present	Ad hoc reviewer, Clinical Gastroenterology and Hepatology
2017-present	Ad hoc reviewer, Hepatology
2017-present	Ad hoc reviewer, Liver Transplantation

Major Academic and Clinical Teaching Responsibilities:

2021-present	Course Director for Biostatistics and Biostatistics Lab for Undergraduate Clinical Scholars Program at University of Pennsylvania
2021-present	Co-Director, Undergraduate Clinical Scholars Program at University of Pennsylvania
2020-present	Course Instructor for EPID-526/527 Biostatistics Lab at University of Pennsylvania
2019-present	Research mentor: Yedidya Saiman (fellow), Sahil Doshi (medicine resident), Jenna Mancinelli (surgery resident), Karen Xiao (medicine resident), Natalie Wong (medicine resident), Yang-Yu Xiao (medicine resident), Kristen Tessiatore (medicine resident), Sarjukumar Panchal (medicine resident), Sara Chapin (medicine resident), Matthew Dukewich (medicine resident), Marya Pulaski (medicine resident), Charles Lu (undergraduate), Chris Shi (undergraduate), Lauren Schaffer (medical resident), Helen Tang (medicine resident), Roy Wang (medicine resident), Celyn Idami (medical resident), Melissa Kaltenbach (fellow), Claire Durkin (fellow), Amanda Bader (surgery resident), Puru Rattan (fellow), Pedro Ochoa Allemant (fellow), Bachir Ghandour (medicine resident), Natalia Parra (medicine resident), Alexandra McCullough (medicine resident), Catherine Mezzacappa (fellow), Anahita Rabiee (fellow), Shalini Bansal (undergraduate), Lina Yagan (medicine resident), Anna Goebel (medicine resident)
2018-2019	Gastroenterology Chief Fellow, Hospital of the University of Pennsylvania
2018-2019	Teaching Assistant, Gastroenterology Medical School Module, University of Pennsylvania
2010-2011	Teaching Assistant, Advanced Biostatistics, Columbia University School of Public Health
2009-2010	Teaching Assistant, Human Anatomy, Stanford University School of Medicine
2005-2008	Tutor, Organic Chemistry, Yale University

Bibliography:

Published Manuscripts:

1. Hecht AL, **Mahmud N**, Chaudhry S, Cao JY, Branigan GP, Lee J, Theiller E, Roggiani M, Friedman ES, Herman L, Gallis BE. Carbohydrate consumption drives adaptive mutations in Escherichia coli associated with increased risk for systemic infection. *bioRxiv* [Preprint]. 2025 Mar 26:2025.03.26.645536. doi: 10.1101/2025.03.26.645536.
2. Bansal S, Bader A, **Mahmud N**, Kaplan DE. Survival and Cost-Effectiveness of Bariatric Surgery Among Patients With Obesity and Cirrhosis. *JAMA Surg*. 2025 Apr 2:e250490. doi: 10.1001/jamasurg.2025.0490.

3. Grady J, Song M, Townsend W, **Mahmud N**, Tapper EB, Parikh ND. A systematic review of noninvasive laboratory indices and elastography to predict hepatic decompensation. *Hepatol Commun*. 2025 Mar 24;9(4):e0675. doi: 10.1097/HC9.0000000000000675.
4. Choudhury A, Kulkarni AV, Arora V, Soin AS, Dokmeci AK, Chowdhury A, Koshy A, Duseja A, Kumar A, Mishra AK, Patwa AK…**Mahmud N**… Sarin SK. Acute-on-chronic liver failure (ACLF): the 'Kyoto Consensus'—steps from Asia. *Hepatol Int*. 2025 Feb;19(1):1-69. doi: 10.1007/s12072-024-10773-4.
5. John BV, Bastaich D, Mezcappa C, Ferreira RD, Hentschel A, Samos A, **Mahmud N**, Taddei TH, Kaplan DE, Serper M, Dahman B. Identifying Metabolic Dysfunction Associated Steatotic Liver Disease Using Natural Language Processing in a US National Cohort. *Am J Gastroenterol*. 2025 Jan 16. doi: 10.14309/ajg.0000000000003321.
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11. Njei B, Mezzacappa C, John BV, Serper M, Kaplan DE, Taddei TH, **Mahmud N**. Mortality, Hepatic Decompensation, and Cardiovascular Outcomes in Lean vs. Non-lean MASLD Cirrhosis: A Veterans Affairs Cohort Study. *Dig Dis Sci*. 2025 Jan 8;. doi: 10.1007/s10620-024-08764-4.
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Abstracts without associated Publications (past three years):

1. **Mahmud N**, Saiman Y, Serper M, Weinberg E, Rothstein K, Goldberg DS. Rate Of Change In Body Mass Index Prior To Liver Transplantation Is Independently Associated With Post-transplant Survival. *American Transplant Congress*. Philadelphia, 2020 May.

Books and Chapters:

1. Liao J, Kanjee Z. *Internal Medicine Evidence: The Practice-Changing Studies*. Wolters Kluwer Health. March 27, 2017. (contributor)
2. **Mahmud N**, Berzin T. *Endoscopic Management of Polyps and Early Malignancy*. Decker Publishing. 2017.
3. **Mahmud N**, Chan W. *Scientific American Gastroenterology, Hepatology, and Endoscopy: Functional Dyspepsia*. Decker Publishing. 2015.
4. **Mahmud N**, Taner B, Ahsan N. *Handbook of Therapeutic Antibodies, 2nd edition: (Ch 47) Basiliximab (Simulect) and Daclizumab (Zenapax)*. 2nd edition. Wiley Publishing. December 2014.
5. Mansen TJ, Gabiola J, all clinical vignettes provided by **Mahmud N**. *Patient-Focused Assessment: The Art and Science of Clinical Data Gathering*. Pearson Publishing. February 5, 2014.

Grant Support:

2024-2026	National Institutes of Health **R03 Award**, University of Pennsylvania, Dr. Nadim Mahmud (PI)
2022-2025	**Investigator Initiated Research Grant**, GRIFOLS, University of Pennsylvania, Dr. Nadim Mahmud (Co-PI)
2021-2026	National Institutes of Health **K08 Award**, University of Pennsylvania, Dr. Nadim Mahmud (PI)
2021-2026	National Institutes of Health **R25 Award**, University of Pennsylvania, Dr. James Lewis (PI)
2021-2022	**McCabe Fund Pilot Award**, Dr. Nadim Mahmud (PI)
2020-2021	ACG **Junior Faculty Development Award**, University of Pennsylvania, Dr. Nadim Mahmud (PI)
2020-2021	Leonard Davis Institute COVID-19 **Rapid Response Grant**, Dr. Nadim Mahmud (Co-PI)
2017-2019	National Institutes of Health **T32 Training Grant**, University of Pennsylvania, Dr. James Lewis (PI)

Exhibit B

EXHIBIT B

MATERIALS CONSIDERED IN THE EXPERT REPORT OF NADIM MAHMUD, M.D., M.S., M.P.H., M.S.C.E.

ARTICLES/PUBLICATIONS:

- 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 2025;48:S27-S49.
- 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025. Diabetes Care 2025;48:S59-S85.
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DEPOSITION TRANSCRIPTS:

- Deposition Transcript of Christopher Ives, M.D. with Exhibits, dated September 14, 2021
- Deposition Transcript of Darryle P. Bullard, M.D. with Exhibits, dated February 13, 2025
- Deposition Transcript of Donald B. Sanders with Exhibits, M.D. with Exhibits, dated October 8, 2021
- Deposition Transcript of Mark Lockhart, M.D., with Exhibits, dated February 13, 2025
- Deposition Transcript of Ralph S. Buckley, M.D. with Exhibits, dated February 7, 2025
- Deposition Transcript of Robert Robichaux, M.D. with Exhibits, dated February 12, 2025
- Deposition Transcript of Samuel Hooks III, M.D. with Exhibits, dated January 29, 2025

EXPERT REPORTS:

- Expert Report of Christopher M. Mele, M.D. with Exhibits, dated March 9, 2025
- Expert Report of Fareeha Siddiqui, M.D. with Exhibits, dated March 10, 2025
- Expert Report of John A. Russo, M.D. with Exhibits, dated March 10, 2025
- Expert Report of William R. Sawyer, Ph.D. with Exhibits, dated March 10, 2025
- Expert Report of Victoria Chernyak, M.D., M.S. with Exhibits, dated April 8, 2025

STAMPED RECORDS:

- GRobertsJr-AMG-000001 - GRobertsJr-AMG-000054; Alabama Medical Group, dated February 18, 2021
- GRobertsJr-BMFP-000001 - GRobertsJr-BMFP-000001; Bay Minette, dated March 12, 2019
- GRobertsJr-BMFP-000002 - GRobertsJr-BMFP-000003; Bay Minette, dated June 1, 2021
- GRobertsJr-BMMAC-000001 - GRobertsJr-BMMAC-000005; Bay Minette, dated February 28, 2021
- GRobertsJr-BMMAC-000006 - GRobertsJr-BMMAC-000007; Bay Minette, dated February 25, 2021
- GRobertsJr-CA-000001 - GRobertsJr-CA-000905; Cardiology Associates, dated February 25, 2021
- GRobertsJr-DCPOA-000001 - GRobertsJr-DCPOA-000001; Death Certificate, dated March 25, 2020
- GRobertsJr-DCPOA-000002 - GRobertsJr-DCPOA-000002; Death Certificate, dated June 10, 2020
- GRobertsJr-DMC-000001 - GRobertsJr-DMC-000106; Diagnostic and Med Clinic, dated May 21, 2021
- GRobertsJr-DMC-000107 - GRobertsJr-DMC-000131; Diagnostic and Med Clinic, dated January 10, 2025
- GRobertsJr-ESMS-000001 - GRobertsJr-ESMS-000020; Eastern Shore, dated March 3, 2021
- GRobertsJr-ESMS-000021 - GRobertsJr-ESMS-000023; Eastern Shore, dated March 18, 2021
- GRobertsJr-ESMS-000024 - GRobertsJr-ESMS-000068; Eastern Shore, dated May 25, 2021
- GRobertsJr-ESMS-000069 - GRobertsJr-ESMS-000070; Eastern Shore, dated July 15, 2021
- GRobertsJr-ESPT-HR-000001 - GRobertsJr-ESPT-HR-000001; Eastern Shore, dated December 13, 2021
- GRobertsJr-ESPT-HR-000002 - GRobertsJr-ESPT-HR-000002; Eastern Shore, dated December 22, 2021
- GRobertsJr-NBFP-000001 - GRobertsJr-NBFP-000012; Pharmacy Records, dated February 23, 2021
- GRobertsJr-PPR-000001 - GRobertsJr-PPR-000152; PPR, dated September 11, 2019
- GRobertsJr-PPR-000153 - GRobertsJr-PPR-000304; PPR, dated March 9, 2020
- GRobertsJr-QueDia-000001 - GRobertsJr-QueDia-000001; Quest Diagnostics, dated February 12, 2021
- GRobertsJr-SouCC-000001 - GRobertsJr-SouCC-000278; Southern Cancer Center, dated November 13, 2020
- GRobertsJr-TH-BD-000001 - GRobertsJr-TH-BD-000055; Thomas Hospital, dated November 23, 2020

- GRobertsJr-TH-BD-000056 - GRobertsJr-TH-BD-000111; Thomas Hospital, dated March 9, 2021
- GRobertsJr-TH-MD-000001 - GRobertsJr-TH-MD-000750; Thomas Hospital, dated February 16, 2021
- GRobertsJr-TH-MD-000751 - GRobertsJr-TH-MD-001500; Thomas Hospital, dated March 4, 2020
- GRobertsJr-TH-MD-001501 - GRobertsJr-TH-MD-002250; Thomas Hospital, dated November 22, 2019
- GRobertsJr-TH-MD-002251 - GRobertsJr-TH-MD-002823; Thomas Hospital, dated January 13, 2020
- GRobertsJr-TH-PD-000001 - GRobertsJr-TH-PD-000001; Thomas Hospital, dated December 11, 2020
- GRobertsJr-TH-RD-000001 - GRobertsJr-TH-RD-000001; Thomas Hospital, dated January 22, 2021
- GRobertsJr-U&OS-000001 - GRobertsJr-U&OS-000086; Urology & Oncology Specialists, dated February 23, 2021
- GRobertsJr-UABHIM-BD-000001 - GRobertsJr-UABHIM-BD-000047; UAB, dated March 18, 2021
- GRobertsJr-UABHIM-MD-000001 - GRobertsJr-UABHIM-MD-000183; UAB, dated March 15, 2021
- GRobertsJr-UABHIM-MD-000184 - GRobertsJr-UABHIM-MD-000402; UAB, dated August 28, 2021
- GRobertsJr-UABHIM-PD-000001 - GRobertsJr-UABHIM-PD-000002; UAB, dated May 7, 2021
- GRobertsJr-UABHIM-RD-000001 - GRobertsJr-UABHIM-RD-000032; UAB, dated February 18, 2021
- GRobertsJr-UABHIM-RD-000033 - GRobertsJr-UABHIM-RD-000034; UAB, dated February 26, 2021
- GRobertsJr-UABKPTClinic-000001 - GRobertsJr-UABKPTClinic-000001; UAB, dated September 17, 2021
- GRobertsJr-UABKPTClinic-000002 - GRobertsJr-UABKPTClinic-000003; UAB, dated September 2, 2021
- ROBERTS-MR-HOOKS-0001 - ROBERTS-MR-HOOKS-0023; Hooks, dated September 11, 2019
- ROBERTS-MR-UAB-0001 - ROBERTS-MR-UAB-0042; UAB, dated August 16, 2018
- ROBERTS-PHARM-NBP-0001 - ROBERTS-PHARM-NBP-0018; Pharmacy Records, dated December 16, 2019